Cleveland Clinic Quarterly

Volume 22
1955

Cleveland, Ohio

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CHRONIC ULCERS OF THE LEG OF VENOUS ORIGIN

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IT is estimated that 600,000 ulcers of the leg are treated annually in the United States—an estimate that is extrapolated from a reported incidence of 15,000 ulcers of the leg treated annually in Denmark.[1] These vast numbers argue a problem, the magnitude of which never has been evaluated in terms of physical disability and economic loss both to the individual and to the community. This study will present the current beliefs and practices in regard to the origin and treatment of the disease.

Classification of ulcers of the lower extremities. On the basis of etiology, six categories of ulcers of the lower extremities are recognized, as follows[2]:

I. Arterial
   A. Organic origin
      1. Arteriosclerosis obliterans with or without diabetes
      2. Thromboangiitis obliterans
      3. Embolic or thrombotic occlusion
      4. Local pressure
   B. Spastic origin
      1. Raynaud's disease
      2. Scleroderma
      3. Frostbite
      4. Local arteriospasm, traumatic or occupational

II. Venous
   1. Varicose ulcers
   2. Phlebitis
   3. Congenital anomalies

III. Specific ulcers
   1. Syphilis
   2. Tuberculosis
   3. Mycosis
   4. Drugs
   5. Vitamin deficiency
   6. Neurotrophic ulcers
   7. Infection
   8. Gout
   9. Regional enteritis
   10. Chronic ulcerative colitis

IV. Posttraumatic ulcers
   1. Occupational
   2. Factitial

V. Blood dyscrasia
   1. Polycythemia
   2. Pernicious anemia
   3. Leukemia
   4. Sicklemia

VI. Malignant ulcers

This study is concerned chiefly with chronic ulcers in the second category: ulcers of the leg of venous origin.

Anatomy and pathogenesis. An understanding of the fundamental anatomy and pathologic physiology is the basis of rational therapy. The venous anatomy of the lower extremity is composed of three systems: a superficial system, a deep system, and one that interconnects between these two by means of perforator or communicating veins. Normally, the three systems contain a varying number of valves that prevent venous reflux of the blood (Fig. 1). The patency of the veins and the competence of the valves assure the successful return of blood from the extremity. With incompetent valves—either as the result of congenital absence or of infection—retrograde flow through the veins occurs and other pathologic changes are prone to follow.

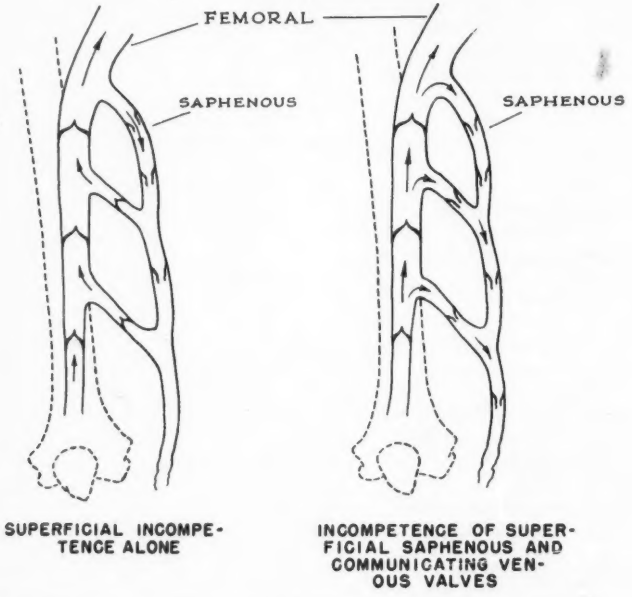

Fig. 1. Types of superficial venous and perforator venous valvular incompetence.

The superficial venous system is composed of the greater saphenous system anteromedially, and the lesser saphenous system posteromedially. The greater saphenous system empties into the deep system at the common femoral vein; the lesser saphenous system is tributary to the deep system at the popliteal vein. The deep system begins in the lower leg as the anterior and the posterior tibial veins which join to form the popliteal vein. In the adductor canal the popliteal vein is known as the superficial femoral vein which unites with the deep femoral vein of the thigh to form the common femoral vein continued in the pelvis to the vena cava as the external iliac vein. Encased in musculo-fascial envelopes, the deep veins dilate only slightly with venous reflux. Hence, when deep-vein valves are incompetent, the reflux of blood flow is forced through the communicating veins into the superficial veins, producing dilatation and subsequently valvular incompetence.

The three systems are intimately associated with the lymphatics that drain the tissue fluids of the extremity. Thus, damage to the veins by infection often is accompanied by lymphatic damage and impairment of drainage of the tissue fluid, resulting in stasis changes.

Stasis changes are those local tissue abnormalities that result from chronic venous reflux and inadequate lymphatic drainage of the area. Centrally in the involved tissue there may be ulceration, surrounding which is a zone of tender, brawny induration known as the zone of stasis cellulitis. Throughout the area are subcutaneous fibrosis and hemosiderin pigmentation that produce a characteristic leathery consistency and tan-to-purple appearance. Often an extensive dermatitis is present, designated as stasis dermatitis (Fig. 2).

Beecher,[3] DeCamp and his associates,[4] Stürup and Højensgard,[5] and others have studied the venous pressures (erect) in the normal leg; in the leg with superficial varices; and in the leg with deep-vein incompetence—that is the "postphlebitic leg." In the resting leg of each (erect) the venous pressure at the foot is equal to the weight of a column of blood from the foot to the level of the right atrium. During walking, in the leg with venous incompetence, whether from superficial varices or deep-vein incompetence, there is constant elevation above normal of the venous pressure (Table). The elevated venous capillary

TABLE

VENOUS PRESSURE (Cm. of H_2O)*

Pressure	Light Exercise, Walking	
	Normal Subjects	Subjects with Varicose Veins
Maximum	75	96
Minimum	28**	96
Resting	63	90
Pulsation	49	0

* *Taken from Beecher.*[3]

** *Persists throughout 2/3 of the step.*

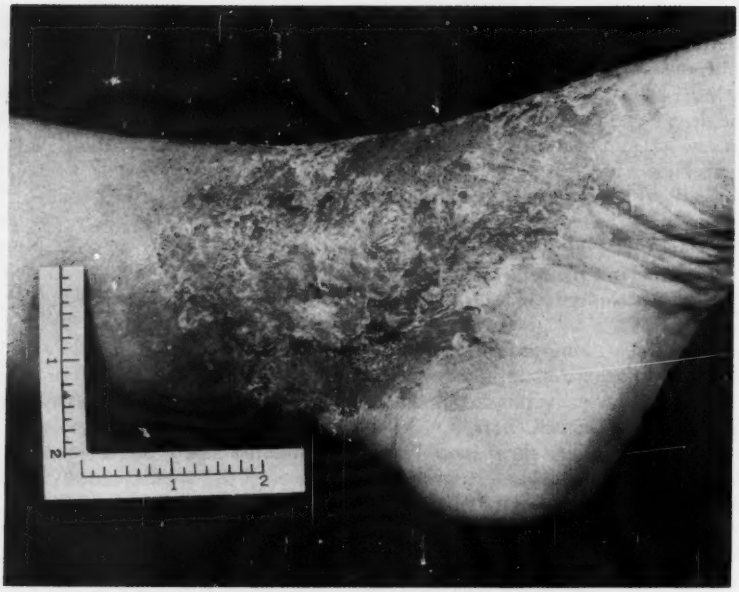

Fig. 2. Stasis dermatitis and ulceration.

hydrostatic pressure then may exceed the colloidal force that normally tends to draw tissue fluid into the capillaries. When the hydrostatic pressure exceeds 60 cm. of water, serum protein is forced into the tissue, thus creating an excess of protein-rich intracellular fluid. Fortunately, the normal lymphatics are capable of rapidly draining away the damaging excess of protein-rich tissue fluid. Hence, if the lymphatics are undamaged, there may be extensive varices with no evidence of stasis change.

The lymphatics, however, often are involved in phlebitis—superficial or deep—and become incapable of removing the excess of protein-rich tissue fluid that collects. Edema then occurs, and the protein-rich tissue fluid not only stimulates fibrosis but acts as an ideal culture medium for infection that furthers fibrosis. As the fibrosis progresses, local blood supply and tissue nutrition diminish, and the slightest trauma or infection is capable of producing ulceration. In the presence of edema there is excessive moisture of the leg and foot, which encourages the growth of fungal and bacterial infections. These infections, once present, produce recurrent lymphangitis with further lymphatic obstruction and also, directly or by antigenic activity, produce ulceration in the tissues damaged by stasis change. Thompson[6] demonstrated that autogenous tricophyton antigens obtained from an infected foot or toenail (athlete's foot) when applied to a distant part of the body could produce a flare of the stasis dermatitis of the leg.

When increased capillary pressure and infection have crucially damaged the

vessel walls, erythrocytes may collect in the tissues and deposit hemosiderin. Unusual pigmentation probably is due to such deposits of hemosiderin.

The pathogenesis of ulcers of the leg that are due to venous incompetence may be summarized as follows: Venous incompetence permits venous reflux with resultant increase in capillary hydrostatic pressure. Proteins diffuse into tissues and, because of inadequate lymphatic drainage, produce edema, stimulate fibrosis, and serve as culture media for infection. Fibrosis and infection result in ulcerations.

Treatment. The objectives of treatment of chronic ulcers of the leg are based on elimination of the five pathologic conditions that have been described, and on prevention of recurrence. Thus, the steps in treatment are elimination of: 1) infection; 2) dermatitis; 3) edema; 4) venous reflux; 5) stasis fibrosis; and 6) prevention of recurrence of ulceration.

Initially, nonoperative treatment is indicated in all patients. Depending upon the severity of stasis changes, ambulation may be permitted, or bed rest may be required.

In the ambulatory patient, the zone of ulceration, the entire leg, and the foot are gently cleansed with phisoderm. The ulcer is then coated with a drying bacteriostatic dye such as a 3 per cent aqueous gentian violet solution, and is covered with fine-mesh gauze and several bulky gauze compresses. To control the edema and provide a bland dressing for the leg, a gelatin boot is applied from the base of the toes to just below the knee, and over this a layer of gauze bandage is fixed with spirals of adhesive tape. The patient is instructed to cleanse between the toes, and around each toenail daily, and to apply an antifungicidal ointment or powder each morning and night. The boot is changed at weekly intervals, with repetition of cleansing and application of gentian violet. The ulcer usually will heal within a few weeks' time. The treatment, however, is continued for several weeks after the ulcer has healed, and thereafter the patient continues to wear an elastic support.

If the ulcer is extensive or so complicated by dermatitis, infection, or edema that ambulatory treatment is not feasible, then bed rest is necessary. The foot of the bed is elevated 4 to 6 inches. The zones of dermatitis and ulceration are gently cleansed with phisoderm, and throughout the day moist saline pressure dressings are applied. At night, a dry, fine-mesh gauze is applied over the area with several layers of overlying compresses, and an elastic bandage is snugly—but not tightly—wrapped from toe to knee. This therapy is continued until healing is sufficiently advanced to permit ambulatory treatment.

Wet saline dressings may aggravate severe dermatitis, and occasionally one must resort to a bland ointment such as vioform ointment or one-half strength coal tar. The use of chlorophyll, antibiotic, or enzyme ointments has not increased the rate of healing significantly; moreover, allergic or chemical reaction may occur and aggravate the dermatitis.

Thus, in the nonoperative treatment, infection is combated by cleanliness and fungicides, and occasional use of systemic antibiotics. The edema is controlled by bed rest and supportive dressings which also act to prevent venous

reflux and congestion. Continuation of support to the leg after the ulcer has healed acts to prevent recurrence of ulceration and progress of the stasis fibrosis.

The operative treatment follows or is combined with the nonoperative treatment. The type and degree of venous incompetence and the patency of the deep veins are determined. A history of postpartum, postoperative, or posttraumatic deep-vein phlebitis is indicative of deep-venous incompetence, as is the presence of incompetent perforating veins. Inspection and palpation of the veins demonstrate superficial varices. The Trendelenburg test and the multiple tourniquet test demonstrate the level of superficial and perforator incompetence. Deep-vein patency is demonstrated by the Perthes' test. Rarely, a venogram may be necessary to establish deep-vein patency. One may assume that one year after an episode of deep-vein phlebitis, recanalization of the vein will have been completed and the deep vein again is patent though it remains incompetent. Ligation of superficial varices is postponed until the deep veins are demonstrated to be patent.

Preoperatively, the greater saphenous system or both saphenous systems and the sites of incompetent perforators and superficial tributaries are marked with the patient erect, using a dye such as 3 per cent aqueous brilliant green. The operation is performed with ligations at the sapheno-femoral junction of the greater saphenous veins and of all tributaries in the area. The main channel of the saphenous vein is stripped using an intraluminal stripper, and then all veins that were marked but not stripped are locally ligated and transected, with particular attention paid to the perforator veins. The lesser saphenous system is treated in similar fashion. The operation may involve 15 to 20 local ligations, over a period of two or more hours, so that general anesthesia is used, or the operation is completed in stages using local anesthesia. Postoperatively, the leg is wrapped from toes to thigh with a snug pressure dressing, and the patient is encouraged to be ambulatory. Sutures are removed seven to ten days postoperatively. The nonoperative treatment of the ulcer is continued until one month after the lesion has been healed.

Successful treatment of deep-vein incompetence by ligation of the popliteal and the superficial femoral veins has been reported[7,8]; however, our own results with these procedures have not been satisfactory.

The large chronic ulcer with stasis fibrosis and marked skin change ultimately will heal with bed rest and ligation of superficial varices; however, it tends to recur repeatedly. In patients having that condition, a wide excision of the zone of ulceration and the zone of stasis fibrosis is performed extending down to the healthy musculo-fascial compartments. The defect is covered with a split-thickness skin graft from the thigh, which provides a healthy skin. These patients must continue to wear elastic supports. If the support proves to be inadequate, by permitting edema to occur with recurrence of ulceration even in the skin graft, then an Aeropulse legging is used.

Aeropulse legging, as described by Merle Scott of Rochester, New York, eliminates the edema and permits rehabilitation and return to work of patients who for several years may have been classified as 100 per cent disabled.

Finally, in the treatment of chronic ulcers of the leg that are due to venous insufficiency, the patient must be impressed with the unpleasant fact that he does not have and never will have a normal leg. He must at all times take such precautions as are necessary to prevent edema and infection, since the presence of either of these conditions will lead to recurrent ulceration. Good elastic support, whether it be a gelatin boot, elastic bandage, elastic stockings, or an Aeropulse legging must be worn during the waking hours. The extremity should be elevated as frequently as possible above hip level. Foot hygiene with control of fungal infection is imperative.

SUMMARY

Ulcers of the lower extremities are classified into six categories according to origin: arterial, venous, specific, posttraumatic, blood dyscrasia, malignant. The pathogenesis of chronic ulcers of the leg of venous origin begins with venous incompetence that is congenital, or arises from trauma or infection. There follow pathologic changes in this order: venous reflux, increased capillary hydrostatic pressure, excess protein diffusion into the tissues, inadequate drainage by the lymphatics, and subsequently edema, fibrosis, infection, and ulceration. Treatment of chronic venous ulcers of the leg initially is nonoperative in all patients. Cleanliness and supportive dressings are indicated, rarely antibiotics. Bed rest also may be necessary. Operative treatment may follow or it may be combined with nonoperative treatment. The patient must be carefully instructed in the care of the extremity: prevention of edema, maintenance of cleanliness, and avoidance of trauma and infection. Where necessary, special elastic or pneumatic supports must be employed.

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THE USE OF NEOMYCIN AND HYDROCORTISONE IN THE TREATMENT OF EXTERNAL OTITIS

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EXTERNAL otitis has been widely discussed in the medical literature,[1-6] but two primary questions concerning the disease have not yet been fully answered: 1) What is the causative mechanism? 2) What is the most effective treatment for resistant cases? The second question is the concern of this report, because we have encountered many severe and resistant cases of external otitis, and our current method of treatment has given uniformly satisfactory results in a series of 57 patients selected for this type of treatment. Some of the patients with recurrences of the disease previously had received most of the antibiotics and the accepted local types of therapy. We do not wish to infer, however, that the newer therapy represents a panacea for all types of otitis externa.

General Considerations

The term "external otitis" implies that there is inflammation of the external ear. Actually in most cases the inflammation is limited to the auditory canal and external meatus, but at times the conchal portion of the auricle or the entire pinna may be involved. The ear drum also may be inflamed or may be covered with granulations.

These external ear infections are universal but more common in the warmer and tropical climates. In the temperate zones, the incidence is high enough to make it one of the most common complaints seen in otologic practice. It is a disease of all ages but seldom occurs in the Negro race. The ear canals of Negroes are shorter, more straight and wider, and, therefore, less favorable circumstances exist for its development. The anatomic structure of the external ear is undoubtedly a factor in the development of infection. The small, tortuous canal offers highly favorable circumstances for the development of infection especially when we consider it terminating in a blind recess. Other contributing factors are undoubtedly the warm, moist contents of the recess which is dark and poorly ventilated.

External otitis can be clinically classified as acute, subacute, chronic, and

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We are indebted to the Upjohn Co., Kalamazoo, Michigan, for providing the drugs used in this study.

recurrent; the objective variations encountered are but graded phases of the same disease.

In the *most severely acute cases*, the patient complains chiefly of intense pain that is aggravated by manipulation of the external auditory canal or by chewing. The auricle may appear uninvolved, but there is frequently periauricular edema and partial or complete obliteration of the canal lumen by the edematous skin of the canal wall. In the remaining lumen are seen purulent secretions, often of various shades of yellow or green, either of thin or of thick consistency, and mixed with exfoliated debris. The patient usually complains of itching of the canals, sometimes intense. Frequently, it is difficult to visualize the tympanic membrane because of a smooth, diffuse sagging of the superior canal wall.

In *chronic cases* there are variable degrees of thickening of the skin of the external auditory canal and of the external auditory meatus which results in reduction of the lumen of the entire canal. Often, the canal is lined with exfoliated debris, either moist or dry, which can be peeled or stripped away by gentle manipulation; or this debris may fill the canal, including the sulcus tympanicus. The drum, or the small portion of it that can be visualized, usually is dull and opaque with loss of light reflex. Usually both auditory canals are involved, but not always to the same degree. Most cases of external otitis occur during the hot summer months but many patients have perennial or recurrent exacerbations of acute infection. Furunculosis of the external auditory canal most frequently develops in patients who have a pre-existing external otitis.

Bacteriology

Bacteriologic studies were made of all our cases; the bacteria were identified and sensitivity tests were made. Previous reports have stated that gram-negative bacilli were the predominant organisms; however, we found that micrococci (both staphylococcus and streptococcus) were predominant in approximately half of our cases. The gram-negative organisms were about evenly divided between *B. coli* and *Pseudomonas aeruginosa*. Other frequent gram-negative organisms were *B. proteus* and *Alcaligenes faecalis*. In this group there were only four fungal infections and all were due to candida. Approximately one half of the patients had been treated previously with many and various topical medicaments and antibiotics; no doubt the bacterial content had been altered in this group. However, in the untreated group, the organisms were about evenly divided between gram-positive cocci and gram-negative bacilli. It was noted that the great majority of the patients in the untreated group had more than one organism present, as proven by cultures taken at the time of the patients' first visits.

Differential Diagnosis

There are many other diseases of the external auditory canal in which the

symptoms may resemble those of external otitis. Brief descriptions of the symptoms of a few of the more common of these conditions follow:

Seborrheic dermatitis. The skin is erythematous, scaly, and greasy; the scalp, eyebrows, nasolabial folds, postauricular skin folds and skin of the neck usually are the parts that are affected. The clinical picture may be obscured by coexistent traumatic excoriations, superimposed infection, crusting, and weeping of the skin, or by changes that have been brought about by overtreatment.

Herpes dermatitis (simplex and zoster). This inflammatory skin disease is characterized by the formation of multiple thin-walled vesicles that cause burning and smarting. In herpes zoster, the eruption of vesicles is unilateral and follows the course of a cutaneous nerve.

Neurodermatitis. This condition is characterized by excoriated, scaly, dry, sharply circumscribed patches with thickening of the skin and increase of skin markings. Other isolated plaques are usually present on skin of the neck, of the eyelids, and of the antecubital areas.

Allergic dermatitis. The skin is erythematous, scaly and excoriated; or it may be vesiculated, hypersensitive, and crusted, with attendant itching and formation of bullae. Skin in various portions of the body including that of the external ear may be involved. Usually the patient has a past history of other allergic diseases, and in some instances there also is a family history of these conditions. Topical medications used on the skin for infection of the external auditory canal are the most common sensitizing agents. This is particularly true of antibiotics, of mercurials, of sulfas, and of local anesthetic agents. Other sensitizing agents include cosmetics, lacquers, perfumes, and jewelry. Unfortunately, improvement does not immediately follow the removal of the offending agent.

Senile skin changes. The skin is atrophied. It frequently is dry, thin, and tan or freckled. Vitamin deficiencies are an etiologic factor, as proved by the frequently beneficial effects of administering vitamin A.

Fungi and yeasts (otomycosis). Several fungi may cause inflammatory reaction in the external auditory canal. There is usually intense itching, but occasionally blocking of the canal by the moldy debris is the only symptom. The color of the molds vary from whitish to black. The two common fungi are the pityrosporum and the several varieties of the aspergillus (niger and flavus). These fungi may cause only a superficial scaling similar to seborrheic dermatitis, or secondary bacterial invaders may be present and the inflammatory changes that develop will completely overshadow the usual appearances in the external canals produced by pure fungal infections.

In these mixed bacterial and fungal infections the fungal component may not be evident until after the bacterial infection has been cleared.

Major dermatopathies. Any of these diseases, such as lupus erythematosus, pemphigus, psoriasis, lichen planus, may involve the skin of the ear canal, but each disease also is manifested by systemic symptoms and evidences of the disease elsewhere in the body. Some of these conditions may be fatal.

Therapy

One of the chief reasons for the failure of treatment in external otitis is inadequate cleansing of the external auditory canal before applying medications. Removal of the obstructing pus and debris permits the selected agent to come into direct contact with the infected tissues. In addition, removal of accumulations from the external canal discourages the propagation of bacteria by creating conditions less favorable for their growth. The suction method, if carefully done without causing trauma, is an excellent method of removing the secretions; it is less time consuming than irrigation of the canal which must be followed by careful drying. The suction technic is best accomplished by using 17-gauge tympanomeatal aspirators bent to the proper angle for good visualization. These aspirators also are extremely effective in removing devitalized epithelium that may remain adherent to the canal walls even after attempts have been made to dislodge it with cotton applicators or by irrigation.

The selection of an appropriate drug to apply to the carefully cleansed canal has been the subject of much controversy. Pharmaceutical houses have been prolific in producing antibiotics and other preparations for topical application; physicians have been liberal in their use of these preparations. Too often the results have been disappointing, and in many instances the patient has been actually made more uncomfortable by the drug because it produced a local skin-sensitivity reaction. This sensitizing reaction frequently has been noted with the sulfa compounds, penicillin, terramycin, aureomycin and streptomycin, when they have been applied locally. The incidence of reaction was particularly high when the drug had been applied to a raw weeping surface. Because of the frequent ineffectiveness of the various recommended drugs and the not infrequent skin-sensitivity reaction, the search has persisted for a more suitable therapeutic agent or combination of agents. An antibiotic having a wide range of effectiveness is necessary for the successful treatment of external otitis. It should effectively combat both gram-positive and gram-negative bacteria; it should have a low tendency for producing bacterial resistance; and it should not cause allergic skin reactions. In the treatment of pyogenic skin infections, dermatologists have found that neomycin is the most effective agent yet produced for topical antibiotic therapy. Its clinical value is greatly enhanced since it almost never causes allergic reactions in the skin. Also it has been shown that when hydrocortisone is applied locally to the skin in cases of skin inflammation, including external otitis, it relieves the inflammation during the administration, but that relapses occur when therapy is discontinued.

The addition of neomycin to hydrocortisone has the therapeutic advantage of controlling the underlying infection due to its antibacterial action, thereby preventing the recurrences that are usually encountered when hydrocortisone alone is used. With the combination of these highly favorable therapeutic agents it seemed obvious that it should be tried in a series of controlled cases of external otitis. This form of treatment for external otitis was started on this series of patients June 18, 1953, and the 57 cases reported include only those that had

cultures and sensitivity studies determined before treatment was begun.

The commercial preparation used was NeoCortef 1.5 per cent suspension and was supplied by the Upjohn Company. NeoCortef is a sterile suspension containing 15 mg. of hydrocortisone acetate, 5 mg. of neomycin sulfate, and 0.02 mg. per cc. of Myristyl-gamma-picolinium chloride (pH_7). The following technic was employed: Cultures were taken from both ears of each patient. The external auditory canals were carefully cleansed by 17-gauge aspirator; care was taken to remove, when possible, the purulent discharge and epithelial debris from the innermost portion of the canal. The NeoCortef suspension was then instilled into the external auditory canal. The patient was instructed to repeat this procedure three times daily at home. (It is easier for the patient to apply the drops when in a reclining position, lying on the side opposite to the one being treated). The solution was allowed to remain in the canal for ten to fifteen minutes. The same procedure may be used for the opposite ear if indicated. Occasionally, the extreme pain in and swelling of the canal wall would not permit cleansing by suction on the patient's first visit; however, it usually was possible after one or two days of treatment.

The suction method of cleansing of the canal probably should be utilized only by the experienced otologist because the canal wall often is extremely sensitive and the slightest amount of manipulation is excruciatingly painful. It is recommended that those less experienced in otology perform a gentle irrigation of the canal and then carefully dry it. In the severe cases with complete or almost complete obstruction of the external ear canal, we recommend that the physician see the patient daily for two or three days, or until the canal can be adequately cleansed and inspected.

Response to Therapy

In our series, the response to this type of treatment was dramatic: patients noted relief from itching almost immediately, with diminution of pain and edema of the external auditory canal and lessening of the discharge within 12 to 24 hours. In most cases there was complete subsidence of all symptoms in five to seven days; rarely was it necessary to continue this treatment for more than seven days. In approximately one half of the cases, mild recurrences occurred in two to six weeks, but in each case there was an immediate response to a second course of the treatment, usually administered by the patient himself at home without an office visit. In the cases of circumscribed external otitis (localized to external auditory meatus), the NeoCortef 2.5 per cent ointment was immediately and uniformly effective, and usually did not require more than five to seven days of treatment. In these cases the ointment used contained 25 mg. of hydrocortisone acetate, 5 mg. of neomycin sulfate, 2 mg. of methylparaben and 1.8 mg. per Gm. of Butylp-hydroxybenzoate. In the majority of the 57 cases not more than two courses of treatment were necessary to get complete relief of symptoms.

Approximately one half of the patients had received treatment before being seen here and in some of them several of the commonly used antibiotics and topical solutions had been administered without improvement. Five of the patients who had been troubled with external otitis for many years had to use the 2.5 per cent NeoCortef ointment before they obtained complete relief without recurrences.

SUMMARY

In this series of cases, the combination of neomycin and hydrocortisone applied topically, either as a suspension or in ointment form was found to be highly effective in the treatment of acute, subacute and chronic external otitis. The incidence of recurrence was also greatly reduced. Repeated courses can be carried out with continued effectiveness and a very low incidence of eczematous contact dermatitis.

The preparations employed appear to be a valuable addition to the therapy of external otitis. They combine the highly desirable anti-inflammatory, antibacterial action with little or no tendency to produce allergic skin sensitivity.

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SARCOMA BOTRYOIDES

Report of Two Cases and Discussion of Nomenclature

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"SARCOMA BOTRYOIDES" is a term that has come to include certain neoplasms of the lower genitourinary tract which occur predominantly in children. Although rare, sarcoma botryoides is the most common lower-urogenital sarcoma found in younger age groups. In boys it arises in the bladder, urethra, and prostate; and in girls in the bladder, cervix, and vaginal vault.

The word "botryoid," derived from a Greek term meaning "like a bunch of grapes," refers to the gross characteristics of the neoplasm: the formation of fleshy, polypoid or grapelike masses. However, the histopathologic findings in sarcomas with these gross characteristics vary. Many of these sarcomas are only indeterminately spindle-celled, and resemble embryonal connective tissue; others of the group contain heterologous mesenchymal elements that most often resemble immature striated muscle cells, and only occasionally resemble cartilage. Thus, on the basis of these histologic variations, these neoplasms have been classified by terms such as "embryonal sarcoma," "rhabdomyosarcoma," and "malignant mesenchymoma."

The problem of nomenclature and classification of the genitourinary sarcomas is not limited to those in the lower urogenital area or to those found in the very young age group. The Wilms's tumor or nephroblastoma of the kidney, the major renal neoplasm of childhood, also can be a heterologous mixture of tissue elements. In women, the malignant, mixed müllerian tumors of the uterus possess many elements usually considered to be of mesodermal origin, such as osteosarcoma, chondrosarcoma, or liposarcoma. The gross characteristics of these müllerian tumors are similar to those of the sarcoma botryoides occurring in the vagina or cervix of a young girl, in that the müllerian tumors often are polypoid and large; however the histopathologic characteristics of the two differ in that the müllerian tumors usually contain malignant epithelial components.

The purpose of this study is to present two cases of sarcoma botryoides that demonstrate most of the features of the polypoid neoplastic process affecting children.

REPORT OF CASES

Case 1

Clinical Features. The patient, an infant girl 17 months old, was seen because two months previously "red bodies" had been expelled from the vagina. The parents stated that the bodies were small, each about the size of a pea. They also had noted a slight amount of associated bloody vaginal discharge.

Physical examination revealed a well-nourished infant with positive findings limited to the genitalia. A polypoid, fleshy, pink mass protruded between the labia majora when they were separated and it apparently filled the vagina. The mass appeared to arise in the upper vaginal vault, but an accurate appraisal of the site of origin was precluded by the size of the neoplasm. The uterus was enlarged as determined by rectal examination. The roentgenograms of the chest and pelvis were normal; the laboratory findings were not significant.

In view of the extensive pelvic involvement, surgery was believed to be inadvisable, and therefore irradiation therapy utilizing both radium and roentgen ray was administered. However, the neoplasm resisted irradiation and the child died 18 months after the first symptoms had appeared.

Pathologic Features. The biopsy specimen consisted of several globoid, translucent, white nodules, ranging from 0.2 to 0.5 cm. in diameter, and arranged in a polypoid configuration.

Microscopic Description. In sections, the masses were composed of a loosely arranged tissue, the surface of which was covered by a thin layer of squamous epithelium (Fig. 1). In areas, small, cleared zones were evident immediately beneath the epithelium, but in others, long interlacing anastomosing cells were present, indistinguishable from mature skeletal muscle elements (Fig. 1a). Centrally in the masses there was a pleomorphic cellular pattern. The predominant cytologic element in the loosely arranged tissue was an elongate cell, at times of almost rectangular shape, at other times the cell was somewhat spindly with pink or red cytoplasm. Many of these cells contained coarse, longitudinal fibrils; some stained with hematoxylin and eosin showed cross striations intensified with the phosphotungstic-acid hematoxylin stain (Fig. 1b). Other cell types encountered included a fairly large and irregularly rounded cell with a homogeneous eosinophilic cytoplasm, and a small spindly form. The nuclei varied in size, but always were vesicular and contained prominent nucleoli; mitotic figures were present.

Case 2

Clinical Features. A 17 month old boy was admitted with a history of intermittent hematuria of three months' duration. The mother stated that initially she had observed drops of blood in his diaper, and tiny, round, pink masses in the urine. No difficulty in voiding had been noted. The infant was asymptomatic for six weeks and then he apparently developed some type of irritating discomfort; at that time the mother noted blood in his diapers on three successive occasions. The child, following the episode of pain, cried with each urination. Two days prior to admission, after straining hard, he passed a small red mass.

External physical examination was normal. Laboratory studies, including blood cell

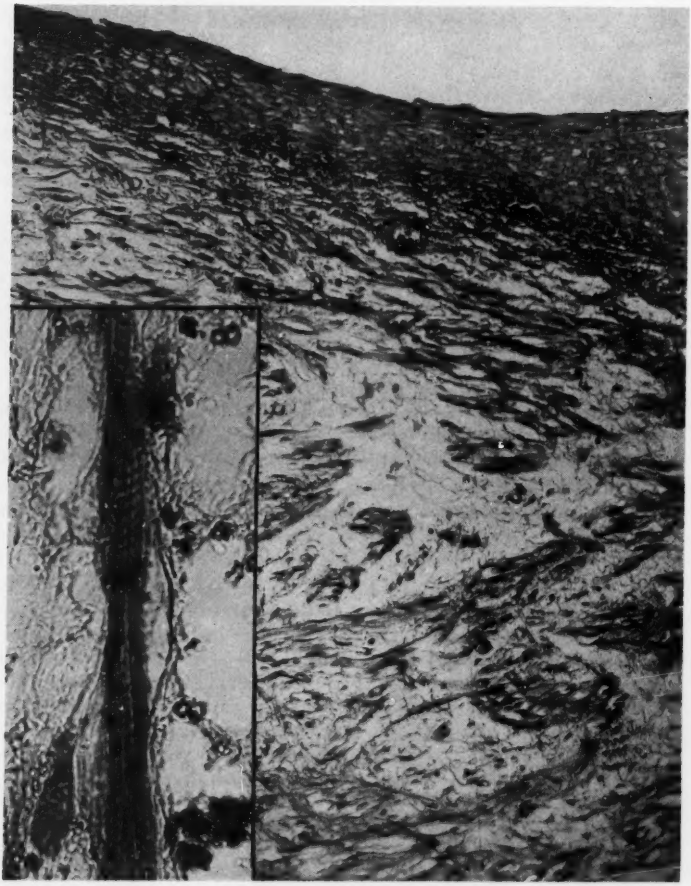

Fig. 1. (Case 1) **a.** Low-power magnification showing small interlacing bundles of elongate cells embedded in a myxomatous stroma. Phosphotungstic-acid hematoxylin stain, X 150. **b.** Prominent cross-striations in a neoplastic muscle cell. Phosphotungstic-acid hematoxylin, X 900.

counts, urinalyses and repeated blood urea tests, were within normal limits. Roentgenograms of the chest were normal.

Cystoscopy demonstrated numerous small polypoid structures within the prostatic urethra; cystograms demonstrated that the base of the bladder was elevated, but filling defects were not visualized in the bladder. The polypoid lesions were completely removed transurethrally, and external irradiation was administered to the urethra and to the base of the bladder both by suprapubic and by perineal ports. Although an adequate urinary stream was maintained and no evidence of a recurrence in the urethra was observed by

Fig. 2. (Case 2) **a.** Gross segment of neoplasm demonstrating the "botryoid" excrescences. **b.** Low-power magnification showing that the submucosal area is relatively acellular. A polymorphous cytology is present more deeply. Phosphotungstic-acid hematoxylin, X 150.

urethroscopy, examination five months later demonstrated a polypoid tumor in the bladder lateral to the left ureteral orifice. This small lesion was removed by transurethral resection, and a second course of roentgen therapy was administered. Eleven months from the date of initial treatment, the patient showed evidences of marked intrapelvic and pararectal extension of the tumor. No local recurrence was noted on cystoscopic examination.

Pathologic Features. The surgically ablated tissue consisted of several segments of tissue up to 1.5 by 1.0 by 0.4 cm., which were irregular in shape, white, and glistening. The external surface of one of these was covered with small white excrescences up to 0.3 cm. in diameter (Fig. 2a).

Microscopic Description. Sections of the globoid masses demonstrated them to be covered by a stratified squamous epithelium. The zone immediately beneath the epithelium was not uniformly hypocellular as is so commonly noted, but instead was composed in part of myxomatous-appearing tissue containing many small spindle cells, and others that had a more reticular appearance (Fig. 2b). Within this area occasionally were very small elongate blunted cells containing a few cross striations. The tissue was not homogeneous; however, occasional areas were relatively acellular. A biopsy of one of these acellular segments only did not suffice for making a definitive diagnosis. The histopathologic changes in the more central portions were spectacular. At first, there appeared to be a confused mass of many types of cells embedded in a myxomatous stroma; actually, certain morphologic patterns became apparent. Many of the cells consisted only of a round, small, vesicular nucleus with very sparse fibrillary cytoplasm. Other cells had essentially the same type of nucleus, but with a much more abundant eosinophilic cytoplasm containing longitudinal fibrils that seemed to flare terminally into separate minute processes. These cells were interspersed with cells of a round or oval form which had nuclei that were both centrally and occasionally eccentrically placed, and had the same type of abundant eosinophilic cytoplasm. This last type of cell has been described by others as being a specific type, although we believe it represents merely a cross section of the eosinophilic elongate form. The final type of cell seen was relatively small and often very elongate. It had much the same shape as the oxyphilic form and, in addition, commonly was multinucleate. The essential difference, however, was in the cytoplasm, which was pale, except for transverse, regularly placed condensations of material that stained brilliantly blue with the phosphotungstic acid-hematoxylin stain. None of the very large tadpole forms were seen which are so characteristic of rhabdomyosarcoma in neoplams of the extremities. The cross-striated cells in this particular tissue showed some tendency to occur in groups and small interlacing bundles. Mitotic figures were few in number.

COMMENT

Considerable medical literature has accumulated covering the general topic of mixed-mesodermal tumors. In 1911, McFarland[1] summarized the world literature on vaginal sarcomas, comprising 101 recorded cases, to which he added one case of his own. In compiling the series, he encountered a total of 119 different descriptive terms. Thirty-four of the cases that had been reported in the previous 57 years he accepted as examples of sarcoma botryoides.

A resurgence of interest concerning sarcomas of the lower urogenital tract has been evidenced by the recent literature. Mostofi and Morse,[2] and Ober and Edgcomb[3] divided the records of the cases filed in the Armed Forces Institute of Pathology. Mostofi and Morse[2] limited their study to ten examples of polypoid

rhabdomyosarcomas (sarcoma botryoides) found in the bladder, and Ober and Edgcomb[3] presented the overlapping study defined as "sarcoma botryoides in the female genitourinary tract," including three of the cases previously reported by Mostofi and Morse.[2] Sternberg, Clark and Smith[4] reported 21 cases under the term of "malignant mixed müllerian tumor" (mixed-mesodermal tumor of the uterus). However, two of these 21 cases occurred in children and lacked the neoplastic epithelial component seen in the tumors of women; these two should more properly be classified as "sarcoma botryoides."

The terminology used in diagnosing the lesions always has been a subject for discussion. Many of the terms have been based either on gross or on microscopic characteristics. If one uses the term based on the gross features, "sarcoma botryoides," the grapelike polypoid excrescences are the only features that must be seen for diagnosis. McFarland[5] in a later study was able to accumulate records of 74 vaginal tumors, 77 vesical neoplasms, and 48 prostatic growths, with such a gross characteristic, most occurring in patients less than 22 years of age. On the other hand, the terms "mixed mesodermal tumor" and "malignant mesenchymoma," although based on histopathologic findings, also are relatively indeterminate. Some of the polypoid lesions in children are not mixed in type so far as can be determined, but are composed of only spindle or stellate cells. A purist would consider all of the neoplasms of the uterus and renal parenchyma embryonically to be mesenchymomas. However, strict adherence to rigid histopathologic criteria may produce compartmented groups that closely resemble each other in their biologic behavior. If cross-striated cells are found in a tumor of the bladder, the neoplasm has been put in the category of the rhabdomyosarcomas of the bladder, a rare group in which less than 25 cases have been recorded. Nevertheless, there is a possibility that many tumors classified in the literature merely as "sarcoma botryoides" may have had such distinguishing cells which were not apparent because of their sparsity. McFarland[5] graphically describes the long search necessary at times to find the cells with cross striations. Because of the difficulty in histopathologic identification we believe that sarcomas of the bladder, prostate, and the lower female genital tract, which are closely related, are appropriately included in the term "sarcoma botryoides," that has come to be favored for this group of polypoid tumors found in young people.

The problems of pathogenesis have been widely discussed in many articles on this subject. The cited references contain brilliant discussions of the pathogenesis. The possibility of misplaced cell rests, variable relationships between stroma of the cervix and endometrium and epithelial components, and totopotentiality of neoplastic cells all in turn have been defended and doubted. We have relegated the debate to the background at the present time as being a philosophical problem.

Therapy either in the form of partial excision or of irradiation has been unsatisfactory. Early diagnosis and radical surgical removal of the tumor seems to offer the best hope for the patient's long survival. Long survivals occasionally have been reported in the relatively few cases that have been treated by this procedure. A course of such therapy has a sound basis and is favored, as the

neoplasms appear to be slow to metastasize. Only one of the ten cases reported by Mostofi and Morse[2] showed evidence of metastases; most of the deaths were associated either with inanition or with secondary urinary tract difficulties. It is possible that death occurred before metastases became evident; however, this biologic behavior is in sharp contrast to the widespread dissemination of the mixed uterine tumors of the older age group. Unfortunately, neither of these two cases presented were believed to be favorable for surgical treatment.

SUMMARY

Two cases of sarcoma botryoides have been reported occurring in children; one in an infant girl, involving the lower genital tract; the other in an infant boy, involving initially the prostatic urethra and later the bladder. Although histopathologically both neoplasms contained cross-striated cells, we have not subclassified them as "rhabdomyosarcomas," but have classified them with "sarcoma botryoides," favoring this term as including all such lesions found in children.

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MANAGEMENT OF INFLAMMATION OF THE MAXILLARY SINUS

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INFLAMMATION of the maxillary sinus is a disease that is common despite the current widespread use of the many new antibiotic agents. A systematized approach to the management of this disease, an approach that is useful not only to rhinologists but also to physicians in general, is outlined in this paper. Although the discussion is limited to maxillary sinusitis, many of the aspects discussed are common to other types of sinusitis as well.

Etiology and Classification

The predisposing factors of inflammation of the maxillary sinus may be grouped as follows:

Local—A. Vasomotor rhinitis
1. Allergic
2. Metabolic
3. Chemical
4. Mechanical

B. Septal deformities
C. Turbinate abnormalities
D. Adenoidal obstruction
E. Dental neglect

General—Includes patients having poor hygiene or faulty living conditions or those suffering from chronic debilitating diseases with lowered general resistance, such as diabetes and malnutrition.

The variations in the disorder may be classified as:

A. Catarrhal sinusitis (acute)
B. Suppurative sinusitis
1. Acute
2. Subacute
3. Chronic

C. Hyperplastic sinusitis

The factor actually initiating inflammation of the maxillary sinus usually is an acute rhinitis such as that which accompanies the common cold, influenza, exanthemas, exacerbation or acute onset of allergic rhinitis, and dental sepsis. An estimated 10 per cent are initiated by spread of dental sepsis, either spontaneous or induced by dental manipulation.

Diagnosis and Treatment

Catarrhal sinusitis (acute). Acute catarrhal sinusitis ordinarily is not differentiated from the acute rhinitis which it commonly accompanies. The patient having acute catarrhal sinusitis may state that he has a cold that is more severe and more prolonged than usual. The symptoms are those of rhinorrhea, nasal obstruction, dull headache or pressure sensation, low-grade fever, and malaise. Roentgenograms taken at the height of an acute rhinitis frequently will show a haziness of the sinuses.

The indications are for treatment of the acute rhinitis, with nasal shrinkage, analgesics, antihistaminics (if an allergic factor is suspected), antibiotics (if the reaction is severe), and preferably also rest in bed and general supportive measures.

Suppurative sinusitis (acute). Patients having acute suppurative sinusitis often believe that they have a toothache and they may consult their dentists first. Pain is referable to the teeth, the malar bone, or the forehead on the affected side. Jarring, or chewing, accentuates the pain. Deep pressure or percussion over the antrum produces pain. Pus usually is seen in the nasal fossae or adherent to the pharyngeal wall, unless the ostium is blocked and nasal drainage is prevented. The turbinates are swollen and hyperemic. In addition to complaining of pain, the patient may complain of purulent discharge, nasal obstruction, and headache. Chills and fever alternately may be present. Transillumination is dark on the affected side. Roentgenograms show diffuse clouding in the region of the antrum or perhaps show the presence of a fluid level. Rarely the patient has an acute septic reaction accompanied by edema and redness of the cheek and edema of the lower eyelid; when these symptoms are present, the clinician should suspect a coexistent diabetes or a sinusitis of dental origin.

The indications, as in acute catarrhal sinusitis, are for conservative management, especially at the onset, with rest in bed, analgesics or narcotics as necessary, nasal shrinkage, and adequate antibiotics. Relief of pain usually can be obtained by shrinking the nasal tissues to promote drainage. Severe pain should be relieved promptly by administration of codeine or morphine, or the patient may seek help elsewhere. Conservative management usually is indicated for the first week of the disease. If the patient does not respond to conservative management or if the pain increases, antral irrigation becomes mandatory.

Suppurative sinusitis (subacute). The term "subacute" has come to have dual meanings. Some physicians define subacute as 1) relating to the duration of the disease; others define subacute as 2) relating to the severity of the disease. The first meaning usually denotes that the symptoms have existed for more than ten days but for less than six weeks. The second meaning usually denotes that from the onset the symptoms are mild, with no febrile response, and discomfort is minimal because of fairly adequate drainage. Perhaps the typical case would be that of the patient who phrases his complaint as "a persistent cold"; the symptoms began three to five weeks previously; there is purulent nasal discharge,

and over the antrum there is dull discomfort that is particularly noticeable on bending the head downward or on jarring the area.

Conservative management, as in the other types of sinusitis previously discussed, usually produces a successful result. Nasal decongestants are employed, aided by one or more irrigations to evacuate the purulent antral contents. The course of the disease in many of these cases undoubtedly is shortened by the administration of antibiotics, the use of which, however, is not mandatory.

In the treatment of acute and subacute suppurative sinusitis, it must be remembered that subsidence of the acute symptoms cannot be considered a cure. One should not discharge the patient from observation until objective evidence of cure is demonstrated in the form of normal transillumination, normal roentgenograms, and clear returns from lavage. Antibiotics frequently give temporary symptomatic relief but when administration of the drugs is interrupted there is a prompt flare-up.

Suppurative sinusitis (chronic). More cases of chronic antral suppuration than of any other suppurative sinus disease are seen in clinic practice. It is noteworthy that in cases of chronic antral suppuration it is not the symptoms of pain and headache that bring the patient to the physician; furthermore, frequently nasal symptoms are mentioned by the patient only in answer to the physician's specific questioning. The symptoms that the patient describes as a presenting complaint are related to the chronic purulent drainage from the antral cavity: 1. Postnasal discharge that is removed by hawking and coughing and that usually is most abundant after the patient has been lying down for a period of time. 2. Anterior nasal discharge is a less common complaint. 3. Persistent nasal stuffiness on the affected side because of mucosal engorgement produced by the discharge. 4. Bad odor or taste of the discharge, or the complaint of bad breath. 5. Anorexia. 6. Occasional nausea and vomiting while attempting to clear the discharge. 7. Repeated minor sore throats or chronic pharyngeal irritation. 8. Persistent or recurrent hoarseness. 9. Intermittent or constant tubal obstruction occasionally with serous otitis media, recurrent acute otitis, or chronic otitis with conductive deafness. 10. Rarely, remote symptoms where the antrum may be acting as a focus. All physicians occasionally have seen patients in whom cure of chronic antral suppuration has relieved asthma, rheumatic symptoms, recurrent urinary tract infections, and other remote conditions.

The condition of chronic suppurative sinusitis is suspected on the basis of the history and of the visualization of the discharge, and it is confirmed by transillumination, by roentgenograms of the sinus, and most importantly, by diagnostic antral lavage.

Occasionally, the symptoms will be alleviated following a series of antral irrigations, but this is not the common course. Antibiotics generally are not useful except as an adjunct to surgery. The procedure usually required is the creation of an adequate nasal antral window to assure ventilation and drainage. This procedure is successful in the vast majority of cases.

Attention also must be directed towards eliminating any predisposing factors, such as: nasal polyps, septal deformities, turbinate hypertrophies, associated allergic edema, and dental sepsis.

There are times when suppuration persists because of irreversible mucosal disease, presence of antral septa with inadequate drainage, cicatricial obstruction of the antral window, or presence of a foreign body. In these cases the Caldwell-Luc procedure (the radical antrum operation) is the one of choice, because the interior of the antrum may be visualized completely, the septa may be broken down, all of the diseased membrane may be removed, foreign bodies may be extracted, and a more adequate nasal antral window may be created.

Persistent suppuration resulting from antral oral fistulas following dental extraction occasionally is seen; to obtain a satisfactory clinical result, the fistula must be repaired either at the time of the antral operation or at a subsequent procedure.

Hyperplastic sinusitis. The term "hyperplastic sinusitis" covers a variety of conditions in which roentgenograms show a thickened membrane, diffuse clouding, or apparent cyst or polyp formation in the antrum, but antral lavage produces only clear returns or a small amount of mucus. Such a situation may result from: prior antral suppuration with scarring of the mucosa with or without prior surgery; formation of a cyst or polyp in the antrum; from antral fracture with organization of a hematoma; or from a vasomotor rhinitis, usually allergic in nature. Treatment is not required except in the cases arising from vasomotor rhinitis, and in these the therapy is aimed at the vasomotor rhinitis and not at the condition in the antrum.

CONCLUSION

The prognosis of suppurative antral disease is excellent from the cure standpoint except in instances of bronchiectasis where the pulmonary disease cannot be excised. Even in these the patient may be symptomatically improved by reducing the amount of purulent secretions.

BENIGN ULCERS OF THE GREATER CURVATURE OF THE STOMACH

Report of Two Cases

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BENIGN ulceration along the greater curvature of the pars media of the stomach is uncommon. Levin and associates[1] collected from the literature 20 cases of histologically proven benign ulcers of the greater curvature and added one case of their own in 1949. Griffin[2] found 32 cases of proven benign ulceration along the greater curvature in the literature to 1954, and added three cases: two of which were in the antrum and one in the pars media of the stomach. Danstrom, Lowry and Colvert[3] recently reported five cases, all verified by microscopic study. This makes a total of 40 cases of benign, histologically proven, gastric ulcer along the greater curvature, exclusive of autopsy studies, which have been reported.

The percentages of gastric ulcers along the greater curvature that prove to be malignant vary considerably in different series. Silk and associates[4] reported 18 patients with ulcers along the greater curvature, 10 of which were benign and 8 malignant. They commented that benign ulcer along the greater curvature often is associated with duodenal ulcer or with benign ulcer along the lesser curvature of the stomach. Boudreal and associates[5] in a study of autopsy material reported that 47 of 247 gastric ulcers were on the greater curvature and that 23 of these (49 per cent) were malignant. Smith and associates[6] reported that of 12 ulcers described by the pathologist as being along the greater curvature, 8 were malignant; thirteen additional ulcers, however, were described by the roentgenologist as being along the greater curvature. These reports suggest that there is a high ratio of malignancy in ulcerative lesions along the greater curvature of the stomach.

Recently we have observed two patients with benign ulceration along the greater curvature of the pars media of the stomach. Because of the uncommon occurrence of such lesions, and because of the problem as to whether treatment of these lesions should be medical or surgical, we are reporting these two cases.

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CASE REPORTS

Case 1. A 54-year-old man was first seen at the Cleveland Clinic on March 9, 1951, because of epigastric distress that occurred one hour postprandial. The discomfort had been consistently relieved by food and antacids. Ten days prior to examination, the patient had noted two black stools. The past history revealed that in 1943 a thyroidectomy had been performed for hyperthyroidism, and that in 1947 he had had a duodenal ulcer that had responded promptly to medical treatment.

Findings on physical examination were normal. Laboratory studies revealed the hemoglobin to be 14 Gm./100 ml. Gastric analysis, with alcohol as a stimulant, showed 32 units of free and 46 units of total acidity. On roentgenographic examination of the stomach an ulcer crater, 1.2 cm. in diameter and .7 cm. in depth, was visualized along the greater curvature of the pars media; there was an incisura opposite the ulcer crater and the duodenal bulb was deformed (Fig. 1, a and b). An ulcerating neoplasm was suspected.

Surgical treatment was advised, and on March 26, 1951, 15 days after initial examination, a subtotal gastric resection was performed. At operation, two gastric ulcers, each 8 mm. in diameter, were apparent. Each ulcer was "punched out" with concave, yellowish-tan, irregular bases and with the mucosa heaped up at the edges. A bandlike area of depressed, congested, gastric mucosa connected the two ulcers, one of which was situated 1 cm. from the lesser curvature on the posterior wall, and the other of which was located along the greater curvature. Multiple microscopic sections disclosed no evidences of malignancy.

The patient had an uneventful postoperative course until two months after the gastric resection when he suddenly developed acute appendicitis. A gangrenous appendix was immediately removed. When the patient was last seen on September 12, 1954, more than three years after the gastric resection, he was well although he had some dietary idiosyncrasies.

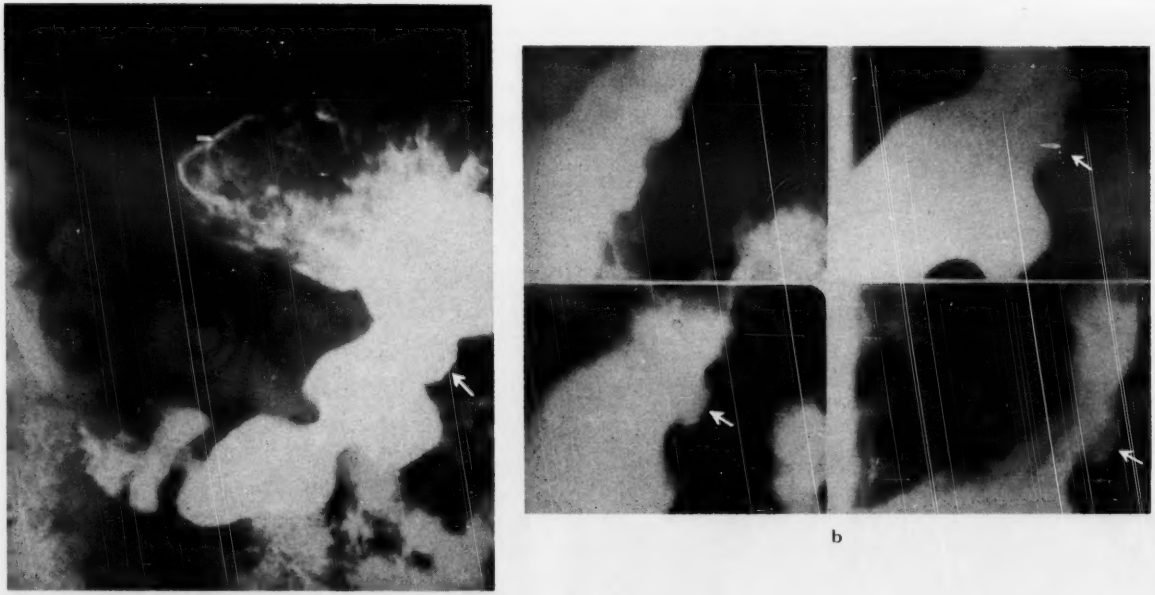
Comment: In view of the observation of Silk and his associates[4] that benign ulcer of the greater curvature often is associated with duodenal ulcer or with benign ulcer of the lesser curvature, the history of duodenal ulcer and the second ulcer near the lesser curvature in this patient are interesting.

Case 2. A 60-year-old woman was admitted to the hospital on March 19, 1954, with a two-month history of postprandial bloating and belching. Three weeks before admission she had developed nausea and vomiting. Her appetite had been poor and she had lost 20 pounds in weight.

Findings on physical examination were essentially normal but the blood pressure was 200/120 mm. Hg. Laboratory studies showed a moderate anemia: hemoglobin was 9.2 Gm./100 ml.; red blood cell 4,140,000, and white blood cell count 7400 per cu. mm. Stools were positive for occult blood. Gastric analysis, with alcohol as a stimulant, showed 26 units of free and 36 units of total acidity.

Roentgenographic studies (Fig. 2, a and b) were reported as follows: the chest was normal except for a slight cardiac enlargement. The stomach was distended and contained food. The distal part of the stomach, for an area of about 5 cm. was markedly constricted in its entire circumference. A small ulceration was thought to be present at the proximal part of this constricted area on the greater curvature. Diverticulosis of the colon was the only abnormal finding on cholecystograms and barium enema studies. The preoperative diagnosis was: annular ulcerating neoplasm of the prepyloric part of the stomach.

Surgical treatment was advised, and subtotal gastric resection was performed on March 25, six days after admission. Gross examination of the stomach revealed four



a b

Fig. 1. (Case 1) Benign gastric ulcer.

a. Roentgenogram showing ulcer (arrow) along the greater curvature of the mid-portion of the stomach. The ulcer near the lesser curvature is not visualized. **b.** Multiple spot films showing the ulcer along the greater curvature (arrow). Again the ulcer near the lesser curvature is not visualized. There is a suggestion of a meniscus sign and an apparent filling defect just distal and proximal to the ulcer. The appearance and the location of the ulcer suggested that it was malignant.

The roentgenograms were supplied through the courtesy of **Dr.** *John R. Hannan, 10515 Carnegie, Cleveland, Ohio.*

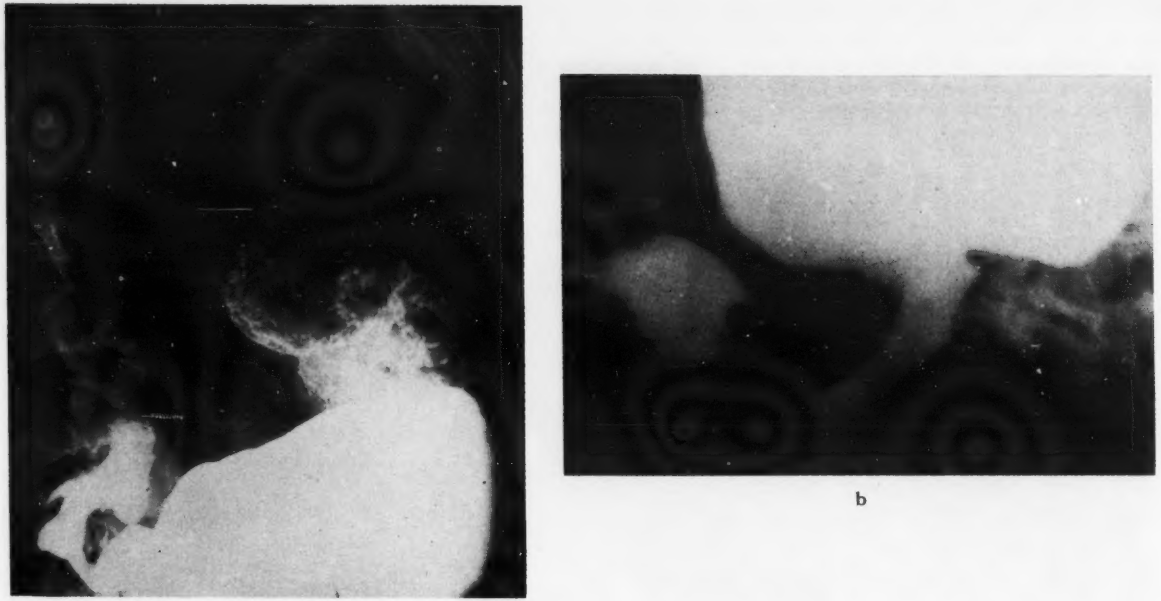


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Fig. 2. (Case 2) Multiple benign gastric ulcer.

a. Barium meal roentgenogram showing marked deformity of the distal antrum, suggesting an annular constricting neoplasm.

b. Spot film of the antrum of the stomach showing marked narrowing of the antrum, most compatible with neoplasm. The four gastric ulcers are not visualized. Ulceration in the stomach may cause marked antral spasm and even gastric retention due to the spasm, even though the ulcer may be in the upper two thirds of the stomach. The spasm of the antrum, as in this case, may simulate carcinoma.

ulcers. Two ulcers (2 cm. and 2.5 cm. in diameter, respectively) were situated on the greater curvature of the stomach just proximal to the antrum. The other two ulcers, each 0.3 cm. in diameter, were "kissing" ulcers, one located on the anterior wall and the other on the posterior wall just proximal to the antrum. Multiple sections of the ulcers revealed no evidence of malignancy, nor was there any evidence of malignancy in the antrum or in the pylorus.

The patient was discharged from the hospital ten days after the operation. She had an uneventful postoperative course and when last seen, six months after surgery, was entirely asymptomatic.

Comment: The deformity in the antrum of the stomach, which on roentgenographic study was strongly suggestive of malignant neoplasm, resulted from spastic phenomena secondary to the four gastric ulcers. Marked spasm of the antrum of the stomach, and even gastric retention, can occur in association with an ulcer higher in the stomach. We have seen several patients each of whom had gastric retention caused by spasm of the pylorus and antrum that was associated with gastric ulceration near the cardia of the stomach.

Of the four ulcers in this patient, only one had been roentgenographically visualized.

DISCUSSION

Each of these patients had benign ulceration along the greater curvature of the pars media of the stomach, and each had multiple gastric ulcers, one having two and the other four. In each case, the multiplicity of the ulcers was discovered only at operation and their benign nature subsequently was established by histologic study. Both patients had been advised to undergo surgery because of indications of possible malignancy on roentgenographic and other clinical examinations. Gastroscopic examinations were not performed because we believed that, on the basis of other evidence, surgery was warranted regardless of possible gastroscopic findings.

We have shown previously that malignant transformation of benign gastric ulcers does occur, but that such transformation is rare.[7] The problem of gastric ulcers is not whether a specific ulcer will become malignant, but whether it is malignant now—that is, the differential diagnosis of benign and malignant ulcers. For typical benign ulcers along the lesser curvature, we believe that a trial of adequate medical treatment with a careful follow-up is indicated.[8]

Many authors (e.g. references 9, 10, 11) advocate surgical treatment for every lesion of the greater curvature of the stomach because of the high incidence of malignancy. Bockus[11] stated that a benign ulcer niche rarely projects from that region in the usual roentgenograms, and he advocated considering and treating all such lesions as malignant. Kennedy and Beck[9] stated that only after histologic examination of the resected lesion is it possible to determine diagnostically that ulceration of the greater curvature of the stomach is benign.

The possibility of gastric malignancy of the greater curvature cannot be excluded or confirmed by roentgenographic examination, by gastroscopic examination, or even by inspection of the stomach at operation. We have seen several cases in which frozen sections at the time of operation showed no evidence

of neoplasm, but permanent sections later disclosed the carcinoma. Consequently, if any findings from clinical, roentgenographic or gastroscopic examination are suggestive of neoplasm, surgical treatment should be advised. The high incidence of carcinoma along the greater curvature necessitates that all such lesions be regarded and treated as malignant.

SUMMARY AND CONCLUSIONS

1. Benign ulcer along the greater curvature of the pars media of the stomach is uncommon.

2. Two cases of benign ulcer of the greater curvature are presented. Both patients had multiple gastric ulcers.

3. Because of the high incidence of neoplasm and the low incidence of benign ulcer along the greater curvature of the stomach, we believe that surgery is indicated for all lesions located in that region.

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SOME RECENT DEVELOPMENTS AND TRENDS IN CLINICAL ENDOCRINOLOGY*

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THE purpose of this presentation is not to give you endless statistics or to recite details of endocrine therapy which readily can be gathered from any of half a dozen, good, recent, endocrinology textbooks. Rather, I wish to offer you a broad over-all view of developments in the laboratory as well as in the clinic—to gain, if we can, a perspective of the trends—to see where endocrinology seems to be going.

THE HYPOTHALAMUS

For many years it has been clearly recognized that the pituitary function is greatly influenced not only by the function of the other endocrine glands and the over-all nutritional status of the body, but also by the nervous system—especially the hypothalamus. These facts have been pointed up particularly well by the work of Hume[1] in this country, and Harris[2] in England. Recently, a piece of information has been reported of new, and I think important, experimental work. Slusher and Roberts[3] have made extracts from the brain and from the hypothalamus that stimulate the anterior pituitary. One, a lipoid extract from the posterior hypothalamus, when injected produces an ACTH-like effect if the pituitary is intact, but if the animal tested has been hypophysectomized no such effect is seen, thus demonstrating a hormonal stimulation of the anterior pituitary.

THE PITUITARY

Anterior Lobe

The extensive investigations concerning hormones of the anterior lobe of the pituitary continue to be directed toward resolving questions such as: Does ACTH have two components, one which affects growth of the adrenal and the other function? What is the true nature of growth hormone? How does it correlate with other factors and, what is the mechanism by which it acts? What is its relation to growth? to healing? to cancer? The answers to such questions should become of great use to clinical practice.

For many years, in this country and abroad, a tremendous amount of effort has been exerted in an attempt to unravel the secrets of the growth hormone. It

* *From an Address presented at the Dallas Academy of Internal Medicine, Dallas, Texas, on October 12, 1954.*

has been reported to have various metabolic effects—such as those of fat mobilization, pancreatic stimulation, anti-insulin or glycostatic activities. Whether these metabolic effects are separate factors or are a part of a complex effect of one natural hormonal protein entity will become apparent only when pure-protein hormone products are available. One of the problems concerning growth hormone which has attracted the greatest attention is how it is related to diabetes. The work of Young[4] and Reid[5] supports the postulation that growth hormone itself may cause lasting diabetes. Raben and Westermeyer[6] reported evidence that the two factors are separable. This apparent discrepancy seems now to have been entirely clarified, however, since Reid showed that the Raben-and-Westermeyer product which produced growth without diabetes at a low pH level is diabetogenic if used at a pH of 10. In this respect it is interesting that at the recent conference on growth hormone in Detroit, Houssay[7] announced that prolactin had a diabetogenic action.

An accurate, expeditious method of assay for growth hormone is much needed. Kinsell, Michaels and Larsen[8] attempted to measure growth hormone in the blood of acromegalic patients by the method of rat epiphysial cartilage growth, but the correlation apparently was not good. Russell and Coppiello[9] demonstrated some years ago that the injection of growth hormone causes a fall in the levels of amino acid in the blood of nephrectomized rats, but we failed to measure quantities of this hormone in the body of man by this method. It is of interest in this regard that Carballeira and co-workers[10] demonstrated a fall in the amino-acid levels in the blood of man after injection of growth hormone. At the growth hormone conference previously mentioned, Segaloff[11] claimed the ability to measure differences in growth hormone levels at various clinical states. In our own laboratories, Westermeyer[12] recently has shown that as little as 5 micrograms of relatively pure growth hormone preparation can be measured by its ability to force radioactive sulfur into the epiphysis of the hypophysectomized rat.

Methods are being perfected for the bio-assay of several pituitary hormones so that they can be clinically applied. In our own laboratories we are accumulating data on the measurement of the interstitial cell stimulating hormone (ICSH) that, presumably, is identical with luteinizing hormone (L.H.). Hypophysectomized rats are used and the phosphatase content of the animals' prostates is measured and compared to the amount in the prostates of controls. The increase in phosphatase content is dependent upon the amount of androgen produced by the testes, the Leydig's cells of which are stimulated by the injected material.

Dobyns and Steelman[13] recently have found that pituitary extracts containing thyroid-stimulating hormone can be treated in such a way as to separate exophthalmos-producing substance almost entirely from thyroid-stimulating effect. At this time, neither this method of separation nor methods of assay for growth hormone or for ICSH effects have clear clinical applications.

The clinical use of ACTH assays will be spoken of in connection with the adrenal.

In the clinical diagnoses of pituitary failure, the findings of low levels of urinary gonadotrophins and of 17-ketosteroids are useful if interpreted from the standpoint of the whole clinical picture. It should not be forgotten that such tests as testicular biopsy (or the even simpler semen examination) or endometrial biopsy which are available to almost all clinicians make excellent qualitative assays if properly applied.

Posterior Lobe

A recent development concerning the posterior pituitary which will have no *direct* effect on clinical medicine, will almost certainly have an extremely important indirect impact on it. I refer to the announcement that Du Vigneaud and his group[14] at Cornell have succeeded for the first time in synthesizing a protein hormone: pitressin and pitocin. If one protein hormone can be synthesized, then perhaps many hormones can be. It should be possible then to obtain protein hormones in perfect purity and, if desired, possibly in modified form and activity.

Hypophysectomy

Another point, quite removed from the above but pertaining to the hypophysis, is the matter of hypophysectomy in the human being for hypertension, diabetic retinopathy, or as palliation in malignancy. It is a formidable procedure, and a complete hypophysectomy in the human being is difficult to perform. I have seen five patients in whom the procedure was attempted. Malignant exophthalmos was present in two, one of whom had diabetes mellitus and hypertension. One of these patients was operated upon before the days of cortisone; the anterior lobe was purposely damaged, but Simmonds' disease inadvertently was produced. The exophthalmos was greatly improved, but the patient eventually died of pituitary failure. The second patient died of repeated severe arterial thromboses, but she had shown much diminution in exophthalmos within two weeks postoperatively. The other three each had metastatic malignancy, from the breast in two, from the adrenal in the third. Although complete hypophysectomy was attempted, it was found later to be incomplete in all three. Pain seemed to have been relieved in one, but in the other two the disease appeared to have been unaffected. Other experience in this country at Memorial Center, New York Hospital and Sloan Kettering Institute,[15,16] Johns Hopkins, and in San Francisco[17] is still meager. Luft and Olivecrona in Sweden[18] have had the most experience. At the time of the Swedish report mentioned, it included 26 patients. Seven had advanced malignant hypertension; three of the seven died postoperatively, and two patients lived two months and five months, respectively. The mortality rate is high, both from unexplained postoperative cerebral edema and from uncontrollable hypotension with renal failure in patients who had hypertension or diabetes. Luft[19] subsequently re-

ported that Olivecrona had performed hypophysectomies on six patients with severe diabetic retinopathy. Two died; one was greatly relieved; and three were improved. Poulsen's[20] report of a patient having Simmonds' disease seems to prove that diabetic retinopathy may disappear after severe pituitary failure, but few physicians are willing to subject a reasonably well patient to the radical procedure of hypophysectomy and, for the seriously ill, the risk is great and in those with extremely advanced diabetic retinopathy the chance of much improvement in the eye seems remote.

THE THYROID

With regard to the thyroid, one of the interesting recent developments is the recognition by radio-paper chromatography of a new thyroid substance, and its identification by Gross and Pitt-Rivers[21] as Tri-iodothyronine. These workers and others have investigated its effects. Blackburn and his associates,[22] for example, showed its effect in single injections to be about four times as strong as l-thyroxine, though this may not hold for larger doses and continued injections. With one dose, maximum effects are seen in about two days, as compared to nine days for thyroxine. Total decay occurs in about 15 as compared to 24 days for thyroxine.

Though these findings increase our knowledge of the thyroid, it is not clear how they will be very helpful in clinical practice. Werner and associates[23] have used Tri-iodothyronine in a test to compare thyroid function in a normal person with that in a patient having Graves' disease, and have produced evidence that Graves' disease is not of pituitary origin, as has been so generally hypothesized. In the tests, they used huge doses of 2.0 mg. per day, the equivalent of about 45 grains per day of thyroid. Such a dose markedly depressed radioactive-iodine uptake in normal persons in whom it was decreased from 53 to 15 per cent. On the other hand, in those having Graves' disease, the uptake decreased only from 71 to 63 per cent. In these hyperthyroid patients, sodium iodide reduced the protein-bound iodine (P.B.I.) content from 11.3 to 8.5 micrograms per cent, and after this reduction and during iodine therapy, thyroid-stimulating hormone (T.S.H.) quickly raised it again. Werner believes that this fluctuation of P.B.I. content indicates that the iodine acts directly on the thyroid cell and not on the T.S.H. As a test for hyperthyroidism, the procedure may prove very useful. Unfortunately, the diagnosis frequently is in doubt in patients with poor cardiac reserve, and the test has the disadvantage of adding stress to a weak heart; under such circumstances unless it is used with caution, the test may be dangerous.

Interesting supporting evidence of Werner's hypothesis concerning the action of iodine has been presented both by Halmi and associates[24,25] and by Vanderlaan.[26] They have shown that while the release of thyroid hormone is under the influence of T.S.H., the trapping mechanism for iodide is not. In hypophysectomized animals which have been injected with known quantities of T.S.H. and known quantities of iodide, it is the original iodide in the thyroid that regulates the further amount of iodine taken up by the gland. This appears to indicate that normally the iodine uptake for fabrication of hormone is gov-

erned by a mechanism inherent in the thyroid itself, and that quite possibly in Graves' disease the excess production of hormone primarily is a thyroid and not a pituitary abnormality.

Another test of clinical interest but still in the investigative phase is one based on the I^{131} thyroid uptake before and after the administration of 10 to 25 units of T.S.H. It was reported at the American Goiter Association meeting in 1950 by Querido and Stanbury[27] that such a test might be used to differentiate primary myxedema in which there was no response to T.S.H., from hypothyroidism of pituitary origin in which there was a response. Jefferies and associates[28] have investigated this test and believe that it is useful for the purpose mentioned and also to indicate whether persons with low metabolic rates have normal or low thyroid reserves. The test also can be used to assist in corroborating or in excluding the presence of hypothyroidism. In a child especially, it is a great advantage to obtain a prompt estimate. For example, if a child has been treated for a long time with desiccated thyroid under the assumption that hypothyroidism is present, normal function of the thyroid may have been markedly suppressed by the treatment. Theoretically, in such an instance, instead of waiting two or three months to test thyroid function, it may be tested at once. This promises to be a useful test. Dr. Penn G. Skillern of our group is analyzing the results of the test in 72 of our patients. So far our findings have been valid in all cases of primary myxedema. Four patients, each of whom has taken thyroid for a long time and who, we think, do not have myxedema, have not responded to one dose of T.S.H. However, in two patients each having myxedema and pituitary tumor, the increases in uptake were slight: 4 to 11 per cent in one, and 34 to 36 per cent in the other. Perhaps in these two patients the poor responses to T.S.H. are similar to the poor responses to ACTH in patients having pituitary failure, and a priming and second or third doses may be necessary. More time is necessary to evaluate our findings.

So far as tests for hyperthyroidism are concerned, the over-all picture has changed little in recent years. Careful clinical evaluation still outshines all tests, and no combination of tests gives completely accurate results. Determining the basal metabolic rate remains a standard part of examination. In most medical centers I^{131} tracer uptake is used to great advantage in evaluating untreated patients having Graves' disease, and the use of a single tube seems as satisfactory from a practical standpoint as the use of multiple counters. Unfortunately, the test may be invalidated by the previous use of iodine in any of its many forms—sometimes for as long as years after its administration.

Many combinations of I^{131} have been studied as tests for hyperthyroidism. The fact that I^{131} is taken up faster in hyperthyroidism than in euthyroidism has led to the use of the "accumulation gradient." Urinary excretion rates or amounts per 24 hours may be determined. Faster answers to diagnostic questions may be had by the use of intravenous I^{131}. Turnover or clearance rates have been calculated by making repeated measurements over the gland and in the blood and urine. I^{131} precipitable with protein from the plasma may be used and the so-called conversion ratio, that is, the ratio of total plasma I^{131} to serum precipitable I^{131}, also is useful. Most of these methods are time consuming and

not well adapted to routine use in clinic or office practice but, what is more important, with none of them is it possible to escape the overlap of hyperthyroidism and euthyroidism.

Protein-bound iodine (P.B.I.), usually thought of as hormonal and as thyroid iodine, is useful, but the P.B.I. test is difficult to perform and there are unexplained false values usually high but also sometimes low. Perhaps further experience with butanol fractionation may explain some such discrepancies.

Until the cause of Graves' disease can be established, I^{131} therapy appears to be here to stay. It continues to gain in popularity after 14 years of use. We have how used I^{131} in the treatment of more than 1400 patients having hyperthyroidism, most of whom have had Graves' disease. Our rule is to use I^{131} only in patients more than 35 years of age, but our inclination to lower the minimum age limit continues. I^{131} is effective with our method of handling in almost 100 per cent of the patients. It is true that not all patients have been traced, so that some poor results may have escaped our attention, but I know of only one patient in whom the treatment had to be abandoned for surgery. Seventy-five per cent respond fully to one dose, and less than 1 per cent need four or more doses. Hypothyroidism occurs in patients treated with I^{131} about as frequently as it does in patients surgically treated. Transient tetany in one patient has been the only other complication of I^{131} treatment that we have seen.

In nodular goiter, I^{131} treatment is not nearly so satisfactory: larger doses, longer duration of treatment, incomplete disappearance of the goiter, and a slight risk of carcinoma are deterents to its use. According to Crile and Dempsey,[29] the possibility of thyroid carcinoma's being present in multinodular glands in which there is no special reason to suspect cancer is less than 1 in 6000. When surgery is undesirable, I^{131} can be used. We recently have used from 30 to 50 millicuries of I^{131} in a single initial dose as treatment of nodular goiter. Of 10 patients having nodular goiters who each received 50 millicuries of I^{131}, in 9, complete or almost complete control of the disease was obtained within four months. Because it often is stated that one disadvantage of I^{131} in the treatment of nodular goiter is its inability to remove the mass, the impression is that the reduction is size that does occur is not useful. However, it frequently happens that a large nodular goiter may shrink to the point where it is scarcely noticeable. In selecting therapy for patients in whom the risk of surgery is prohibitive, I^{131} treatment should be kept clearly in mind as of value in relieving the pressure symptom from a large goiter in the neck or in the mediastinum.

Although the use of propylthiouracil or methylthiouracil is diminishing in popularity, I believe that they still have a place in treatment. In patients having Graves' disease and small-to-moderate-sized goiters who are treated with the thiouracils, complete control for one to two years is followed in about 77 per cent of the cases by lasting remissions. In patients having very large diffuse goiters or toxic nodular goiters who are operated upon, only 50 per cent have lasting remissions. In young people in the selected group mentioned, thiouracil treatment has the advantage of leaving the thyroid gland intact and presumably normal, and of causing no lasting complications.

There is little new to be said about the treatment of thyroiditis. In the subacute form, cortisone may relieve symptoms till the disease abates; or symptoms may subside rapidly under propylthiouracil. Struma lymphomatosa, when suspected and diagnosed by needle biopsy, may largely disappear when 3 grains of thyroid is administered daily. The mechanism by which struma lymphomatosa is thus controlled has been explained in a most illuminating study of the disease and I think the most important paper on the subject since the disease was first recognized. Gribetz, Talbot and Crawford[30] showed that in this disorder the P.B.I. may be high and yet there is no hyperthyroidism. This is explained by the fact that the butanol-extractable protein-bound iodine level is not elevated. It seems entirely reasonable to believe that the thyroid under these circumstances is producing an abnormal product incapable of the natural power of pituitary inhibition and that therefore high titers of T.S.H. cause excessive thyroid growth. This hypothesis seems to be corroborated by the finding that thyroxine fed to such patients does not cause a rise but a fall in the level of total protein-bound iodine.

THE PARATHYROIDS

In regard to the parathyroid glands, two points come to mind: The first is that Grollman[31] has just reported that the administration of parathyroid hormone is effective in nephrectomized animals, a finding that seems to settle the long-standing controversy as to whether the hormone reacts solely on the renal tubule. The second point concerns hyperparathyroidism and the Howard-intravenous calcium test. Dr. Robert Schneider of our group—has used the test in 30 patients in whom hyperparathyroidism was suspected. The results in no case proved to be wrong, although several tests gave borderline results that were too difficult to interpret to be useful. In one of the 30 patients, the Howard test was positive and hypercalcemia persisted, but surgical exploration revealed no adenoma in the neck. Exploration of the mediastinum disclosed a tumor on the aortic arch. In our last patient operated upon recently, the outcome has not been so fortunate. Although the patient had a positive Howard test, persistent hypercalcemia, and hypercalciuria, exploratory surgery of the neck and mediastinum revealed no tumor.

THE PANCREAS

With regard to the pancreas, there is only one point I wish to mention. You may not all be acquainted with the fact that the hormone glucagon—the hyperglycemic glycogenolytic factor (H.G.F.) of the pancreas—has been definitely isolated, crystallized, and its component amino acids have been defined. Intravenously, it causes a sharp rise in the level of blood sugar, which lasts about one hour. It apparently is the first normal line of defense against hypoglycemia.

Its physiology, its relation to diabetes, and its application to clinical use are being explored.

THE ADRENALS

Adrenal Medulla

With respect to the adrenal medulla and the diagnosis of pheochromocytoma, in addition to the standard tests based on inhibition of adrenalin and noradrenalin (regitine, benzodioxane) as well as provocative tests (histamine), the measurement of urinary products of adrenalin or noradrenalin is proving a very accurate guide. The estimate of catechol amines can be accomplished by chemical, chromatographic fluorometric, or by biologic means. A very accurate method is said to be that of Weil-Malherbe and Bone.[32] Von Euler's[33] method is biologic. Attention is directed to the very valuable paper by Goldenberg and associates[34] on chemical screening methods.

Adrenal Cortex

The clinical status of Addison's disease is not changing rapidly. The best test is the intravenous ACTH test with estimation of urinary 17-hydroxysteroids as well as 17-ketosteroids. The Power-Kepler water-excretion test is simple and, if intelligently interpreted, usually accurate. If doubt exists, the 24-hour excretion of 17-hydroxycorticoids may be measured after intravenous administration of ACTH. In women, the presence of normal neutral 17-ketosteroids in the urine usually excludes the possibility of Addison's disease, though it should be remembered that some normal women have very low levels of 17-ketosteroids. Nowadays, the treatment of Addison's disease with cortisone or hydrocortisone usually is extremely simple, and desoxycorticosterone acetate (D.O.C.A.) or extra salt seldom is needed. Overtreatment with cortisone is to be avoided for fear of suppressing remaining adrenal function. The great disadvantage of the use of cortisone or hydrocortisone in Addison's disease lies in the fact that withdrawal of therapy may be disastrous. Some patients who have lived for many years in poor health because of undertreatment may blossom into apparently excellent health under the effects of small doses of cortisone and suddenly die as a result of the drug's having been carelessly omitted for two or three days.

In mentioning new developments relating to the adrenal cortex, one cannot omit electrocortin, more recently called "aldosterone," discovered in 1952 by Tait, Simpson and Grundy.[35] It is the sodium-retaining factor long known to be a very active constituent of the amorphous fraction of adrenal extracts. It has a sodium-retaining power said to be 120 times as great as desoxycorticosterone[36] and an action at least as great as cortisone in so far as cold stress is concerned.[37] It apparently has little effect on carbohydrate metabolism.

Aldosterone almost certainly is the substance that during the phase of water retention has been shown to be greatly increased in the urine of patients with

cardiac decompensation, cirrhosis of the liver, and nephrosis. It has been identified with certainty in one patient who had episodes of paralysis and high loss of urinary potassium without retention of excess sodium,[38] and more recently has been identified in normal urine.[39,40] In doses of 100 micrograms per day, the hormone has already been shown to have a marked effect on electrolyte balance and a slight effect on carbohydrate metabolism in Addison's disease. It also has the remarkable power of causing rapid fading of the pigmentation present.[41,42]

In a recent issue of SCIENCE (Nov. 5, 1954) in a report of the September Laurentian Hormone Conference, a paper by Tait[43] was mentioned. Tait outlined the methods used for the isolation and identification of aldosterone (electrocortin). He pointed out that aldosterone differs from most of the other adrenal steroids in that it possesses an aldehyde group at C^{13}, has an extremely high sodium-retention potency, has a very small concentration in normal adrenal venous blood, and strangely enough appears to be little, if at all, under ACTH control.

Recently the discovery of a new, interesting, and clinically promising adrenal steroid has been announced.[44,45,46] It is a modification of hydrocortisone in which a halogen is attached in the 9, alpha position. The sodium-retaining and potassium-excreting effects of very small doses (25 to 100 micrograms) of the chloro- and fluoro-derivatives in adrenalectomized dogs are like those of D.O.C.A. Early trials in treating Addison's disease suggest that fluorohydrocortisone is considerably more effective than equimolar quantities either of D.O.C.A or hydrocortisone itself.[47] Unpublished findings from early trials suggest that suitable dosages of fluorohydrocortisone may range from 0.5 to 2.0 mg. per day. Fluorohydrocortisone recently has become available for local use. It has not been found to be as useful as cortisone for treatment of connective-tissue diseases.

ACTH

The assay of ACTH in the blood of man can be made by several methods. A highly sensitive method is that of Sayers and associates.[48] The results of various workers employing Sayers' method have been reviewed by Paris, Upson, and associates.[49] Two outstanding facts appear; namely, that this hormone may be measured in the blood of patients having untreated Addison's disease, but usually not in those having untreated Cushing's syndrome. It has been established that the production of ACTH can be suppressed by cortisone, and the correlation of this fact with certain new developments regarding virilism is important.

One of the most intriguing of recent developments in clinical endocrinology is a clarification of our understanding of virilizing syndromes. We cannot go into the differential diagnosis in any detail now, but let me recall some outstanding points to mind. The clinical manifestations of the virilizing syndrome vary according to age and sex.

In an infant boy having the congenital form of the disease, the penis may be very large; there may be evidence of excess androgen and yet he may be a sodium waster; he may vomit and mistakenly be considered to have pyloric stenosis, and therefore he may die of cortisone deficiency. A similar situation sometimes exists in prepuberal boys. Boys having this condition can be maintained in good health by cortisone.

In infant girls, a congenital defect may produce pseudohermaphroditism; in prepuberal girls, it may produce pubertas praecox with markedly advanced skeletal maturity, and tendency to masculinization; and in women, adrenogenital syndrome. Sydnor and associates[50] have shown that children having this condition have high levels of ACTH in the blood, which is consistent with poor production of cortisone. Many patients with this condition have abnormally high levels of urinary 17-ketosteroids which quickly will fall to normal with cortisone therapy and may be maintained at normal with dosages as small as 25 mg. per day orally.

The subject of virilization has been nicely reviewed by Jailer[51] who with Wilkins and associates[52,53,54] has done outstanding work in clarifying this issue. Jailer points out that in these individuals, ACTH produces an abnormal response: The levels of urinary 17-ketosteroids and pregnanediol go up. There is, however, no increase in 11-oxysteroids as there should be normally, no fall in the number of eosinophils, and no sodium retention. These effects occur normally if compound F is present. What then is the explanation? Hechter and others[55] showed that the normal adrenal can hydroxylate 17-hydroxyprogesterone to compound F; and it had been shown before[56] that 17-hydroxyprogesterone is masculinizing. It thus appears that the enzyme system concerned fails to produce the full metabolic shift that is needed to change 17-hydroxyprogesterone to compound F. Because of the tendency toward underproduction of cortisone and like materials, pituitary ACTH is overproduced. In response to excess ACTH, the adrenal in its attempt to produce enough cortisone-like materials, produces a continued excess of a masculinizing product. (There is still some difficulty with this theory at the moment, because although it was originally reported that 17-hydroxyprogesterone was androgenic, there is now doubt about this.[57]) If this explanation is correct adrenogenital syndrome, excluding that due to tumor, must be classed as an enzyme disease. Cortisone under these circumstances is a highly effective hormone for treatment. For similar reasons such a response may be studied and used in differentiating adrenal hyperplasia from adrenal tumor. In patients with tumor, the typical marked reduction in the level of urinary 17-ketosteroids is less likely to occur.

Adrenalectomy

One last word about the adrenals, and that is concerning the status of bilateral adrenalectomy. Firstly, for control of hypertension: In the Philadelphia series, Jeffers and associates[58] last year reported their findings in 82 patients who had undergone bilateral adrenalectomies and most of whom had had

sympathectomies as well. The adrenalectomies had been performed 1 to 33 months before the report was published. The results were called excellent in 23 per cent; poor in 32 per cent. In the Boston series of Thorn and associates,[59] 15 patients (12 having malignant hypertension and 3 having chronic glomerulonephritis) underwent bilateral adrenalectomies. Five survived more than one year. In only one of these five patients was there definite improvement that lasted more than one year. One patient had improved greatly and returned to work, but 11 months after the operation died of coronary occlusion. Five patients with malignant hypertension resistant to other modes of treatment have been under study by the Research Division before and after bilateral adrenalectomy. Four of these, who were in renal failure, showed no benefit from the operation, which only complicated the rapid and inexorable progress of their disease. The other survived four months, manifesting only slight decreases of average arterial pressure during episodes of adrenal insufficiency and maintaining at other times the severe hypertension from which eventually he died. Secondly, let me mention bilateral adrenalectomy used in an attempt to control metastatic malignancy: This form of treatment largely has been discarded because the administration of cortisone is capable of producing such complete suppression of adrenal function that, usually, adrenal surgery could not improve the results.

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

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THE CLEVELAND CLINIC FOUNDATION

announces the second annual day and one-half postgraduate course of particular interest to general practitioners

February 9 and 10, 1955

The course is open to all members of the medical profession and has been approved for ten hours' credit by the American Academy of General Practice. The subjects are varied and are those of general current interest. Registration will be limited to 100.

Tentative Program

Wednesday, February 9, 1955

Morning Session

8:00- 9:00 a.m.	Registration	
9:00- 9:05 a.m.	Opening Remarks	HERBERT SALTER, M.D.
9:05- 9:20 a.m.	Early Detection of Organic Brain Disease in General Practice	L. J. KARNOSH, M.D.
9:20- 9:35 a.m.	The Diagnosis of Intervertebral Disk	A. T. BUNTS, M.D.
9:35- 9:50 a.m.	Functional Voice Problems	W. H. GARDNER, PH.D.
9:50-10:05 a.m.	The Outlet Syndrome	P. A. NELSON, M.D.
10:05-10:20 a.m.	Surgery of Acquired Heart Disease	D. B. EFFLER, M.D.
10:20-10:40 a.m.	Intermission	
10:40-11:00 a.m.	Jaundice: Diagnosis and Treatment	H. R. ROSSMILLER, M.D.
11:00-11:20 a.m.	Diabetic Acidosis	E. P. MCCULLAGH, M.D.
11:20-11:40 a.m.	Use and Abuse of Steroid Therapy in Common Dermatoses	G. H. CURTIS, M.D.
11:40-12:15 p.m.	Question and Answer Period	
12:30- 2:00 p.m.	Luncheon—Courtesy Bunts Institute	

Afternoon Session

2:00- 2:15 p.m. . Present-Day Management of Infections of the Urinary Tract . . . . . W. J. ENGEL, M.D.

2:15- 2:30 p.m. . Clinical Significance of Hematuria . . . . . C. C. HIGGINS, M.D.

2:30- 2:45 p.m. . Nerve Blocks of Value in General Practice . . . D. E. HALE, M.D.

2:45- 3:00 p.m. . The Significance of Nipple Discharge . . . . A. H. ROBNETT, M.D.

3:00- 3:20 p.m. . Artificial Hibernation . . . . . W. J. KOLFF, M.D.

3:20- 3:40 p.m. . Intermission

3:40- 4:45 p.m. . Panel—Radiation Therapy: X-ray, Radium, Cobalt-60, Radioactive Iodine, Phosphorus, and Strontium, Radium in ENT, Physics . . . . . R. A. HAYS, M.D., MODERATOR
J. D. BATTLE, JR., M.D.
OTTO GLASSER, PH.D.
H. E. HARRIS, M.D.
R. J. KENNEDY, M.D.
E. P. MCCULLAGH, M.D.

Thursday, February 10, 1955

Morning Session

9:00- 9:30 a.m. . The Proctoscopic Examination and Management of Rectal Tumors . . . . . R. B. TURNBULL, JR., M.D.

9:30-10:00 a.m. . Cosmetic Surgery . . . . . ROBIN ANDERSON, M.D.

10:00-10:30 a.m. . The Use and Abuse of Ultra Radical Operations for Cancer . . . . . GEORGE CRILE, JR., M.D.

10:30-10:45 a.m. . Intermission

10:45-11:15 a.m. . Surgical Treatment of Segmental Arteriosclerosis Obliterans . . . . . A. W. HUMPHRIES, M.D.

11:15-12:30 p.m. . Panel—Acute Emergencies in the Upper Abdomen . . . . . R. S. DINSMORE, M.D., MODERATOR
RUSSELL MCGINNIS, M.D. (GUEST)
GEORGE CRILE, JR., M.D.
A. H. ROBNETT, M.D.

GUEST SPEAKER

RUSSELL MCGINNIS, M.D.
Director of Department of Surgery, St. Luke's Hospital,
Cleveland, Ohio.

REGISTRATION BLANK

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Please register me for the course on "General Practice" to be given February 9 and 10, 1955. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, February 9.

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces the following Postgraduate Course from March 21 through 26, 1955, given under the auspices of the American College of Physicians

A postgraduate course on "Pathology and Pathologic Physiology in Internal Medicine" will be given at the Cleveland Clinic under the auspices of the American College of Physicians from Monday, March 21, through Saturday, March 26, 1955. The course will place emphasis on pathologic anatomy and current concepts of pathologic physiology in systemic disease. The principal objective will be to stress the relationship between pathology, pathologic physiology and clinical diagnosis and treatment. The major subjects to be presented will be in the fields of cardiovascular and renal disease, pulmonary disease, gastroenterology, hematology, endocrinology, and metabolic diseases. The course will include lectures, clinical demonstrations, pathology conferences, and question and answer panels.

Tuition fees will be $30.00 for members of the American College of Physicians and $60.00 for nonmembers. Application should be made directly to Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

The Cleveland Clinic is located at Euclid Avenue and East 93 Street. Nearby hotels having comfortable accommodations are the Wade Park Manor, Park Lane Villa, and Alcazar Hotel. We would suggest writing in advance for reservations.

PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE

Tentative Program

Monday, March 21, 1955

8:00- 8:50 a.m. . . Registration

8:50- 9:00 a.m. . . Orientation . . . . . A. C. ERNSTENE, M.D.

HEMATOLOGY

9:00-10:00 a.m. . . Pathology Conference: The Leukemias and Malignant Lymphomas . . . . . J. B. HAZARD, M.D., L. J. MCCORMACK, M.D., AND J. D. BATTLE, JR., M.D.

10:00-10:30 a.m. . . The Macrocytic Anemias . . . . . R. W. VILTER, M.D.*

10:30-10:45 a.m. . . Intermission
10:45-11:30 a.m. . . Iron Metabolism and Iron Deficiency Anemias . . . . . J. W. HARRIS, M.D.*
11:30-12:00 noon . The Hemolytic Anemias . . . . . T. H. HAM, M.D.*
12:00-12:30 p.m. . Question and Answer Panel
12:30- 1:30 p.m. . . Luncheon—Courtesy of the Cleveland Clinic
1:30- 2:00 p.m. . . Blood Coagulation, Purpura, and Hemophilia. J. S. HEWLETT, M.D.
2:00- 2:30 p.m. . . Erythroblastosis . . . . . VIOLA STARTZMAN, M.D.
2:30- 3:00 p.m. . . Abnormal Forms of Hemoglobin . . . . J. D. BATTLE, JR., M.D.
3:00- 3:15 p.m. . . Intermission
3:15- 3:45 p.m. . . Multiple Myeloma . . . . . J. D. BATTLE, JR., M.D.
3:45- 4:30 p.m. . . Vitamin Deficiency Diseases . . . . . R. W. VILTER, M.D.*
4:30- 5:00 p.m. . . Question and Answer Panel

Tuesday, March 22, 1955

ENDOCRINOLOGY AND METABOLIC DISEASES

8:00- 9:00 a.m. . . Pathology Conference: Diseases of the Pancreas . . . . . J. B. HAZARD, M.D., L. J. MCCORMACK, M.D., P. G. SKILLERN, M.D., AND GEORGE CRILE, JR., M.D.
9:00- 9:30 a.m. . . Principal Pathways of Intermediary Metabolism . . . . . ARNOLD LAZAROW, M.D.*
9:30-10:00 a.m. . . Hypoglycemia . . . . . P. G. SKILLERN, M.D.
10:00-10:15 a.m. . . Intermission
10:15-11:00 a.m. . . Experimental Diabetes . . . . . ARNOLD LAZAROW, M.D.*
11:00-11:30 a.m. . . Hyperparathyroidism—Primary and Secondary . . . . . R. W. SCHNEIDER, M.D.
11:30-12:00 noon . Pathology of Diseases of the Thyroid Gland . . . . . GEORGE CRILE, JR., M.D.
12:00-12:30 p.m. . . Question and Answer Panel
12:30- 1:30 p.m. . . Luncheon—Courtesy of the Cleveland Clinic
1:30- 2:00 p.m. . . Iodine Metabolism and the Action of Antithyroid Drugs . . . . . V. W. WESTERMEYER, M.D.
2:00- 2:30 p.m. . . The Changing Status of Hyperthyroidism . .R. S. Dinsmore, M.D.
2:30- 3:00 p.m. . . Myxedema . . . . . P. G. SKILLLERN, M.D.
3:00- 3:15 p.m. . . Intermission
3:15- 3:45 p.m. . . Clinical Aspects of Disturbed Pituitary Function . . . . . W. MCK. JEFFERIES, M.D.*
3:45- 4:30 p.m. . . Management of Diabetic Acidosis and Coma . . . . . E. P. MCCULLAGH, M.D.
4:30- 5:00 p.m. . . Question and Answer Panel

Wednesday, March 23, 1955

ENDOCRINOLOGY AND METABOLIC DISEASES

8:00- 9:00 a.m. . . Pathology Conference: The Adrenals, Ovaries and Testes . . . . . J. B. HAZARD, M.D., L. J. MCCORMACK, M.D., AND E. P. MCCULLAGH, M.D.
9:00- 9:30 a.m. . . Diagnosis and Treatment of Pheochromocytoma . . . . . D. C. HUMPHREY, M.D.

9:30-10:15 a.m. . . Disturbances of Adrenal Cortical Function. E. P. McCullagh, M.D.
10:15-10:30 a.m. . . Intermission
10:30-11:00 a.m. . . Therapeutic Effects of Estrogens and Androgens . . . . . R. W. Schneider, M.D.
11:00-11:30 a.m. . . Gout . . . . . W. S. Clark, M.D.*
11:30-12:00 noon . The Alarm Reaction and Adaptation Syndrome . . . . . A. C. Corcoran, M.D.
12:00-12:30 p.m. . . Question and Answer Panel
12:30- 1:30 p.m. . . Luncheon—Courtesy of the Cleveland Clinic

GASTROINTESTINAL DISEASE

1:30- 2:15 p.m. . . The Management of Peptic Ulcer and Its Complications . . . . . E. N. Collins, M.D.
2:15- 2:45 p.m. . . The Differential Diagnosis of Jaundice . . H. R. Rossmiller, M.D.
2:45- 3:15 p.m. . . Sprue and Sprue-like Syndromes . . . . . C. H. Brown, M.D.
3:15- 3:30 p.m. . . Intermission
3:30- 3:50 p.m. . . Urological Disease as a Cause of Gastrointestinal Symptoms . . . . . E. F. Poutasse, M.D.
3:50- 4:15 p.m. . . Medical Management of Chronic Ulcerative Colitis . . . . . E. N. Collins, M.D.
4:15- 4:30 p.m. . . Surgical Treatment of Chronic Ulcerative Colitis . . . . . R. B. Turnbull, Jr., M.D.
4:30- 5:00 p.m. . . Question and Answer Panel

Thursday, March 24, 1955

8:00- 9:00 a.m. . . Pathology Conference: Diseases of the Liver . J. B. Hazard, M.D., . . . L. J. McCormack, M.D., and H. R. Rossmiller, M.D.
9:00- 9:30 a.m. . . Amebiasis . . . . . C. H. Brown, M.D.
9:30-10:00 a.m. . . Systemic Lupus Erythematosus . . . . . J. R. Haserick, M.D.
10:00-10:30 a.m. . . Rheumatic Fever—Pathogenesis, Treatment, and Prevention . . . . . R. D. Mercer, M.D.
10:30-10:45 a.m. . . Intermission
10:45-11:15 a.m. . . Rheumatoid Arthritis . . . . . A. L. Scherbel, M.D.
11:15-12:00 noon . The Hyperventilation Syndrome. . . . . L. L. Lovshin, M.D.
12:00-12:30 p.m. . . Question and Answer Panel
12:30- 1:30 p.m. . . Luncheon—Courtesy of the Cleveland Clinic

CARDIOVASCULAR AND RENAL DISEASE

1:30- 2:00 p.m. . . Arteriosclerosis Obliterans and Thromboangiitis Obliterans . . . . . F. A. LeFevre, M.D.
2:00- 2:30 p.m. . . Diagnosis and Treatment of Segmental Arteriosclerosis Obliterans . . . . . A. W. Humphries, M.D.
2:30- 3:15 p.m. . Pathogenesis of Essential Hypertension . Harry Goldblatt, M.D.*
3:15- 3:30 p.m. . . Intermission
3:30- 4:00 p.m. . . Newer Concepts in the Treatment of Hypertension . . . . . Roland Schneckloth, M.D.
4:00- 4:30 p.m. . Fluid and Electrolyte Balance. . . . . Harriet Dustan, M.D.
4:30- 5:00 p.m. . Anuria and Uremia . . . . . W. J. Kolff, M.D.
5:00- 5:30 p.m. . Question and Answer Panel

Friday, March 25, 1955

CARDIOVASCULAR AND RENAL DISEASE

8:00- 9:00 a.m. . . Pathology Conference: Renal Diseases . . . J. B. HAZARD, M.D., ... L. J. MCCORMACK, M.D., AND D. C. HUMPHREY, M.D.
9:00- 9:30 a.m. . . Pathogenesis of Atherosclerosis . . . . . I. H. PAGE, M.D.
9:30-10:00 a.m. . . The Pathogenesis of Congestive Heart Failure . R. N. WESTCOTT, M.D.
10:00-10-15 a.m. . . Intermission
10:15-11:00 a.m. . . Dynamics of Aortic Insufficiency . . . . . C. J. WIGGERS, M.D.
11:00-11:30 a.m. . . Pulmonary Function Tests . . . . . R. N. WESTCOTT, M.D.
11:30:12:00 noon . . The Mechanism of Edema . . . . . C. J. WIGGERS, M.D.
12:00-12:30 p.m. . . Question and Answer Panel
12:30- 1:30 p.m. . . Luncheon—Courtesy of the Cleveland Clinic
1:30- 2:00 p.m. . . Pathologic Physiology of Congenital Heart Disease . . . . . F. M. SONES, JR., M.D.
2:00- 2:30 p.m. . . Diagnosis and Treatment of Cardiac Arrhythmias . . . . . J. F. WHITMAN, M.D.
2:30- 3:00 p.m. . . Treatment of Congestive Heart Failure . . W. L. PROUDFIT, M.D.
3:00- 3:15 p.m. . . Intermission
3:15- 3:45 p.m. . . Thrombophlebitis and Its Complications . . V. G. DEWOLFE, M.D.
3:45- 4:00 p.m. . . The Post-Phlebitic Syndrome . . . . . A. H. ROBNETT, M.D.
4:00- 4:30 p.m. . . Biopsy of the Lung and Pericardium as Diagnostic Procedures . . . . . H. S. VAN ORDSTRAND, M.D.
4:30- 5:00 p.m. . . Question and Answer Panel

Saturday, March 26, 1955

CARDIOVASCULAR AND PULMONARY DISEASE

8:00- 9:00 a.m. . . Pathology Conference: Diseases of the Lungs . J. B. HAZARD, M.D., . L. J. MCCORMACK, M.D., AND H. S. VAN ORDSTRAND, M.D.
9:00- 9:30 a.m. . . Angina Pectoris . . . . . A. C. ERNSTENE, M.D.
9:30-10-15 a.m. . . Prognosis in Coronary Artery Disease . . . . R. W. SCOTT, M.D.*
10:15-10:30 a.m. . . Intermission
10:30-11:00 a.m. . . Management of Bacterial Endocarditis . R. A. VAN OMMEN, M.D.
11:00-11:30 a.m. . . Indications for and Results of Mitral Valve Commissurotomy . . . . . D. B. EFFLER, M.D.
11:30-12:00 noon . . Question and Answer Panel

* *Guest speaker.* (*Affiliations listed on page 57.*)

GUEST SPEAKERS

W. S. CLARK, M.D. — Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

HARRY GOLDBLATT, M.D. — Head of Department of Pathology, Mt. Sinai Hospital, Cleveland, Ohio.

T. H. HAM, M.D. — Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

J. W. HARRIS, M.D. — Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

W. McK. JEFFERIES, M.D. — Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

ARNOLD LAZAROW, M.D. — Professor of Anatomy, University of Minnesota School of Medicine, Minneapolis, Minnesota.

R. W. SCOTT, M.D. — Professor of Clinical Medicine, Western Reserve University School of Medicine, and Physician-in-Chief, Cleveland City Hospital, Cleveland, Ohio.

R. W. VILTER, M.D. — Professor of Medicine and Assistant Dean of University of Cincinnati College of Medicine, Cincinnati, Ohio.

THE CLINICAL USE OF SERUM IODINE DETERMINATION

HELEN B. BROWN, Ph.D. and V. W. WESTERMEYER, M.D.
Research Division

SIMPLIFICATION of the measurement of iodine in body fluids has resulted in increased use of the test and in demonstration of its importance in the study of patients suspected of having thyroid disease. Indeed, under certain circumstances, serum iodine determination may be the only laboratory test that shows with precision the abnormalities of thyroid function.* This is not surprising, since each of the three laboratory tests used in studying the thyroid—basal metabolic rate, thyroidal uptake of radioactive iodine and chemical determination of serum iodine—measures separate aspects of thyroid activity. Furthermore, each of the tests may be influenced by separate extrathyroidal factors. The purpose of this article is to outline the diagnostic uses and limitations of serum iodine determinations.

A simplified scheme (Fig. 1) shows the manner in which dietary iodine is made available for the production of thyroid hormone. In this diagram, it may be seen that the bulk of dietary iodine is first converted to iodide, mixing with the inorganic pool of the body, and then is taken up in part by the thyroid gland.

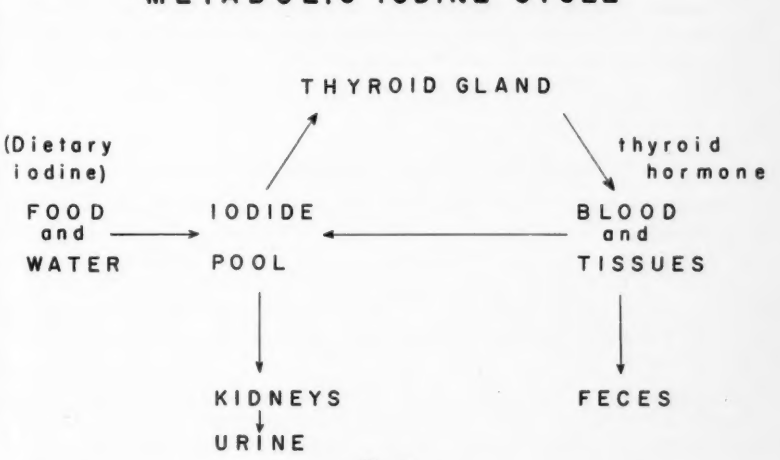

Fig. 1

**Representative reviews of iodine metabolism,[1] thyroid physiology[2] and clinical use of blood iodine determination[3] have appeared in recent years.*

The remainder is made available for renal excretion. Besides the urinary excretion of iodide, an additional small proportion of body iodine is excreted as thyroid hormone glucuronide in the feces.

In the thyroid, iodine is affixed to tyrosine from which is synthesized the thyroid hormone. The hormone is stored within the gland as thyroglobulin but is released in a free form into the blood stream. Here it circulates combined with serum protein. Its discharge from the thyroid is under the influence of the thyrotropic substance of the anterior pituitary. The amount of this pituitary hormone in the serum is controlled, in turn, by the level of the circulating thyroid hormone. This is an example of the self-regulating relationship between pituitary hormones and their target organs, which is an important factor in endocrine homeostasis.

The Nature of Serum Iodine

From the preceding description of the iodine cycle, it can be seen that iodine is present in the serum in two forms, inorganic and protein bound (Fig. 2A); that inorganic iodide concentration is primarily dependent on dietary content; and that the protein-bound iodine is constituted largely of thyroid hormone which is available to the tissues. Chemically, serum inorganic iodide is entirely dialyzable, acid and water soluble. By precipitation, it may be easily separated from the clinically more significant protein-bound iodine. The protein-bound iodine consists almost entirely of thyroxine with traces of the more active triiodothyronine, and the biologically inactive diiodotyrosine. These substances are so weakly bound with serum protein that they easily dissolve in butanol. The diiodotyrosine accompanying thyroxine into the butanol is removed by washing with strong alkali. The remaining material is largely thyroxine and has been loosely termed the "butanol-extractable iodine" (BEI).[4]

Clinical Use of Serum Iodine Measurements

The minute concentration of serum iodine causes its determination to be a more difficult procedure than most other clinical laboratory procedures. However, it is not prohibitively tedious, and even the recently introduced fractionation of the protein-bound iodine does not place undue burden on the analyst. Both inorganic and protein-bound iodine should be determined routinely while the butanol fractionation of the latter need be done only when it will be of diagnostic value.

Because of the rapidity with which it is removed from the circulation, the inorganic iodide usually amounts to only a few micrograms per hundred milliliters of serum. It is not a direct measure of thyroid function. Nevertheless, it is of great value to the clinician since high values offer a clue to previous uses of iodine-containing substances, an historical point that patients are notoriously poor at recalling. Furthermore, it is well to remember that the inorganic fraction

may be falsely elevated by tincture of iodine used as a skin antiseptic prior to venipuncture.

The protein-bound iodine, of course, is the more important of the serum iodine fractions since its concentration usually parallels that of circulating thyroid hormone. Four to eight micrograms per hundred milliliters of serum is present in euthyroidism while values greater than 8 or perhaps 9 micrograms are found in hyperthyroidism, and less than 3 or 4 in myxedema. These normal limits, however, are not always clear-cut and must be evaluated in relation to other clinical information.

In certain cases, the protein-bound iodine values do not correctly define thyroid function. For example, elevated values unassociated with hyperthyroidism are found in certain cases of thyroiditis,[5] following radiation injury of the gland and after administration of iodine-containing substances [4,6-9] for therapeutic or radiologic purposes (Table). In most instances of abnormal values due to use of iodine compounds, the contamination appears in a butanol-insoluble fraction as shown in Figure 2B. The presence of this butanol-insoluble iodine leaves the thyroxine-like (butanol-soluble, alkali-insoluble) fraction as a precise measure of circulating thyroid hormone.

Abnormally low values of protein-bound iodine may be found in euthyroidism. Thus, patients who have hypoproteinemia do not sustain normal serum iodine concentrations, presumably because there is insufficiency of iodine-

TABLE
Sources and Duration of Artifactual Values of Serum Iodine

Substance	Source: Procedure	Duration of effect	Remarks
Diodrast[6]	Urography[7]	4 weeks[7]	Unpredictably elevated[6]
Priodax *[6]	Cholecystography[7]	3 months[7]	Very high[6]
Pantopaque[6]	Bronchography[7]	9-12 months[7]	Elevated
Lipiodal[6]	Myelography[7]	1-5 years[7]	Unpredictably elevated[6]
Radioactive iodine	Destruction of thyroid tissue[8]	6-8 weeks	Elevated
Lugol's solution[4]		2-6 weeks	Elevated
Potassium iodide[9]		6-8 weeks	Elevated
Mercuhydrin[11]		24 hours	Lowered

**Priodax yields a butanol-soluble complex.*

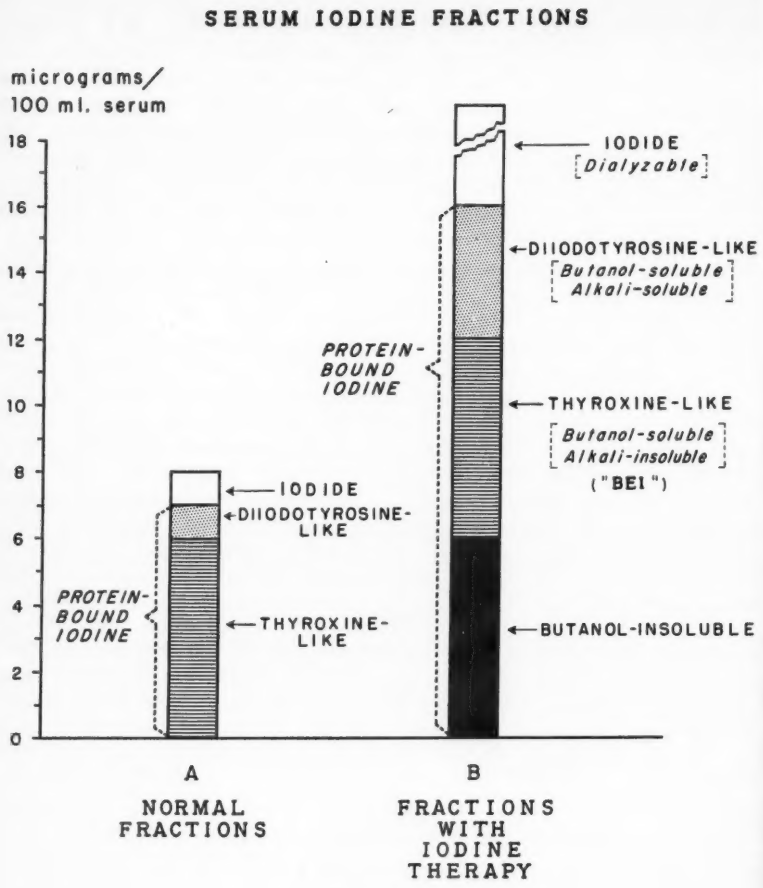

Fig. 2

carrying protein.[10] Falsely low values are found in patients receiving mercury-containing compounds, because iodine is removed by mercury during the chemical determination.[11]

In general, the unfractionated serum protein-bound iodine will indicate the true nature of the disease in hyperthyroidism and hypothyroidism as well as does the B.M.R. However, the protein-bound iodine is much more than a check on clinical judgment in uncomplicated cases. It fills a particular need as a precise measure of thyroid-hormone concentration in the serum. An example of the precise use of the test is in a case of factitious hyperthyroidism. Here, the

thyroidal uptake of radioactive iodine is low because of the antithyroid effect of large doses of thyroid substance and provides a false clue to thyroid status. However, the elevated serum protein-bound iodine will correctly measure the endocrine defect. Another example of the specific use of the test is in the study of thyroidectomized patients suspected of having recurrent thyrotoxicosis. In these cases, radioactive iodine uptake may be high even in the presence of euthyroidism; furthermore, the B.M.R. may be elevated because of the presence of other diseases that simulate hyperthyroidism. The serum protein-bound iodine, however, will furnish a true evaluation of the state of the thyroid.

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THE "CURABILITY" OF OVARIAN CARCINOMA

JAMES S. KRIEGER, M.D.
Department of Gynecology

IN 1826, William P. Dewees, M.D., Adjunct Professor of Midwifery at the University of Pennsylvania, wrote of the ovaries in his *Treatise on the Diseases of Females*[1] as follows:

> They seem to be removed so far from the general sympathies of the system; so insulated in position; so independent in function; that the common agents for the removal or control of disease, seem to waste themselves in unavailing attempts to influence their actions or modify their affections. Who flatters himself that he has removed a dropsy, resolved a scirrhus, or interrupted a suppuration in these bodies? We believe, if he be candid, none will confess he has, little more then at present is ascertained than that they are very liable to disease and but very little susceptible to cure.

In the 129 years since Doctor Dewees' comments were published, we have made great strides in medicine and surgery. We now are able to cope with suppurations and, on occasion, control the function of the ovaries—but what of our progress with dropsy and scirrhus? Our knowledge about these diseases has increased greatly, and we seemingly are able to cure a significant number of patients. However, are we doing as well as we think we are?

Recent literature on ovarian carcinoma is confined mainly to statistical analyses of large groups of cases, with a general sameness of conclusions. These statistics allow us to draw the following profile in regard to ovarian carcinoma: The woman afflicted with ovarian carcinoma may be of any age, though most frequently she is 40 years of age or older. Symptoms, when present, tend to be protean and to have existed for an average of eight or nine months. The correct diagnosis is suspected preoperatively in 50 to 55 per cent of patients; at surgery, 40 per cent of patients have inoperable carcinoma. Carcinoma involves both ovaries in 30 to 50 per cent of the cases and the uterus in 6 to 8 per cent of cases. Munnel,[2] and Pearse and Behrman[3] have been unable to demonstrate any correlation between the duration of pretreatment symptoms and the length of survival. Throughout the country the five-year survival rate approximates 15 to 20 per cent, with a progressive decrease in the number of these survivors as the years pass. As a matter of fact, more women are dying of ovarian carcinoma today than did 20 years ago. This chiefly results from increased life expectancy secondary to improved treatment of nonneoplastic diseases and from better recognition of ovarian carcinoma. It is readily apparent that our therapeutic efforts in this disease leave much to be desired. Indeed, we are not controlling

"dropsy and scirrhus" today. On the basis of present knowledge and employing available diagnostic and therapeutic tools, can we improve the situation?

Symptoms and Diagnosis of Ovarian Carcinoma

The classical symptoms of ovarian carcinoma consist of abdominal pain, increase in abdominal size, abdominal mass, loss of body weight, and occasionally vaginal bleeding. Since symptoms tend to be protean and late in occurrence, increased awareness of them is unlikely to increase the possibilities of accurate early diagnosis.

Improved patient education. It has been suggested that a program of better education of the patient is desirable. The significance of abnormal vaginal bleeding and new and unusual vaginal discharge is now fairly well appreciated, yet few women understand the need for periodic examination when no symptoms are present. Certainly it would seem that if women were to be examined more frequently we should be able to diagnose cases of ovarian carcinoma at earlier stages of development. However, as previously stated, the correct diagnosis is suspected preoperatively in only 50 per cent of cases, and at surgery 40 per cent of the total are inoperable. This should make us a bit less complacent in following supposedly benign conditions. With an adequate educational program we shall need to improve our diagnostic acumen.

Diagnostic aids. The Papanicolaou smear and the cervical biopsy aid in early diagnosis of cervical carcinoma. Bleeding is a common symptom of corpus carcinoma; and curettage, a relatively innocuous procedure, may be employed to make the diagnosis. In ovarian carcinoma, there are no early symptoms and no simple diagnostic tests available. It has been suggested that the employment of culdoscopy or culdotomy in suspected cases might make earlier diagnosis possible. Unfortunately, a cross section of the tumor usually is necessary, and often a diagnosis can be made only via microscopy. Papanicolaou smears of cul-de-sac washings would reveal only far-advanced tumors that were sloughing cells, and therefore would be of no value in early diagnosis.

Thus, in diagnosing ovarian carcinoma we are primarily dependent on our palpatory ability. A postmenopausal woman with an enlarged ovary, or a menstruating woman with a cyst larger than 5 cm. in diameter, presents no problem in therapeutic approach—operation is indicated. However, a menstruating woman with an enlarged ovary less than 5 cm. in diameter, presents a very difficult problem; we cannot and should not routinely subject such a woman to laparotomy. Instead we "follow" the cyst, waiting to see whether it will persist or will disappear. A certain percentage of those women will have carcinoma, and metastases well may occur during this interval of observation. MacFarlane and associates[4] in performing periodic routine pelvic examinations on 537 women over a 15-year period discovered six patients with ovarian carcinomas, of whom one is alive four and one-half years after therapy.

Early diagnosis. As mentioned previously, Munnel,[2] Pearse and Behrman[3] have been unable to find any correlation between duration of pretreatment

symptoms and length of survival. Pearse and Behrman[3] further have pointed out that when the diagnosis is made only after pathologic examination of excised specimens, survival rates are not necessarily improved—only 13 of 39 such patients survived five years.

Therapy

Present therapy consists of various combinations of surgery and irradiation—the treatment of choice being total hysterectomy and bilateral salpingo-oophorectomy followed by postoperative irradiation.

As previously stated, with present diagnostic efforts, 40 per cent of patients who come to operation are found to be inoperable. Extending the scope of surgery by performing radical or supraradical procedures will not materially increase the salvage in this disease since extrapelvic metastases often occur before demonstrable local spread (this tendency to metastasize early may in part be due to the peculiar blood supply of the ovaries).

All other available therapies fall into the palliative category. Omentectomy is a desirable routine procedure but is very unlikely to be curative. Radioactive gold and nitrogen mustard are helpful in selected cases, since they produce an adhesive peritonitis, thereby decreasing the rate of formation of ascites. Preoperative irradiation occasionally will make an inoperable lesion amenable to surgery.

Prophylactic Removal of Ovaries

Since the majority of cases of ovarian carcinoma occur after the age of 40 years, it has been suggested that any woman having a pelvic operation for benign disease after this age should have both ovaries removed. Since according to Randall[5] the incidence of ovarian carcinoma never exceeds 9 in 1000 women, and since in Allan and Hertig's[6] series only 22.6 per cent of women having ovarian carcinoma had been subjected to previous pelvic surgery, this approach seems unduly drastic and likely to reduce the rate of incidence only slightly. The ovaries, also, have been shown to have a function after the menopause; consequently the routine removal of them would seem unreasonable. Incidentally, since carcinoma is bilateral in 30 to 50 per cent of cases, the fallacy of unilateral oophorectomy as a prophylactic procedure becomes apparent.

CONCLUSION

It is apparent on the basis of the above discussion that increased awareness of symptoms and periodic pelvic examination performed on the asymptomatic patient will not make earlier diagnosis possible, since the diagnostic methods available to us are totally inadequate. Our therapeutic methods are likewise inadequate, since even with early diagnosis the rate of survival is not necessarily improved.

It has been suggested that the crux of the problem lies with an unfortunate anatomic location of the ovaries which allows them to undergo malignant

transformation without being observed. This concept suffers when applied to the breast and testicle. Both of these organs are admirably located for inspection, palpation, and seemingly early diagnosis, yet in spite of our efforts, survival rates for patients with carcinomas in these locations are notably poor. Were the ovaries located as are the testicles would the salvage rate be changed? We suspect that it would not.

It is apparent that our hope for the eventual control of ovarian carcinoma is very similar to that expressed by Doctor Dewees 129 years ago:

> But must we so humble the powers of the healing art, as to declare, we never shall be master of their [ovaries] diseases! Certainly not. Advances are constantly making towards at least the improvement, if not the perfection of the art; and we are now and then made acquainted with substances, which have a specific action upon certain tissues of the human body. The time may then arrive when we shall be in possession of a remedy whose agency shall be confined to the ovaries alone, or to similar organizations, if such there be, in other portions of the system. But until then, unfortunately, the victims to affections of these important parts, must remain contented with the solace which palliatives may afford.

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REHABILITATION PROGRAM FOR LARYNGECTOMEES, ILLUSTRATED BY FOUR CASE REPORTS

WARREN H. GARDNER, Ph.D.
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Audiology and Speech Pathology Section

LARYNGECTOMIZED patients, known as "laryngectomees," are confronted with two interrelated problems: the acquisition of a substitute for speech, and economic and social rehabilitation. The basic problem is, of course, the acquisition of a substitute for speech.

Since the first laryngectomies were performed about 100 years ago, many artificial devices have been designed and recommended to enable the patient to communicate again. However, in 1909 Gutzmann[1] first described the development of natural esophageal speech in patients who had had their larynges removed. Further studies considered the various factors involved in the acquisition of that form of speech by laryngectomized patients.[2-13] It was fully realized that the psychologic aspects of the operation greatly influenced the patient's chances of learning to talk again. Stern[3] urged that a patient who had had his larynx removed, be encouraged and reassured during the immediately postoperative period by a visit from a former patient who had mastered esophageal speech. Kallen[4] advised that speech therapy be instituted immediately after healing in order to prevent social maladjustment and psychologic depression. Schall[6] and Morrison[9] emphasized the importance of combatting the depression that overwhelms the patient when he realizes that his speech will not be the same as it was preoperatively, and that social and economic readjustment may be difficult. McCall[11] advocated preoperative training for esophageal speech. Yet, despite these recommendations, Pitkin[13] has found that in a group of 65 laryngectomized patients: 87 per cent had not been given adequate speech instruction before operation; 46 per cent had not received hospital visits from other laryngectomees; and 40 per cent had not been adequately prepared for the operation or informed concerning the loss of voice that would follow.

The rehabilitation program for the patient who is to undergo laryngectomy here, begins preoperatively as soon as the physician advises that surgery is necessary. The contributions of the physician and his associates in giving encouragement to the patient and his family and in sharing information on details concerning the forthcoming operation are supplemented by the routine use of four aids that we have found to be of great value in hastening and assuring the patient's rehabilitation: (1) a motion picture, (2) records, (3) a booklet, and (4) visits from those who have undergone the operation and who have learned to talk again.

Motion picture. As soon as possible after the patient has been informed of the necessity of laryngectomy, he and his family are shown the motion picture entitled, *New Voices.*[14] *New Voices* is the story of a man who casually mentions to his physician that he has had a hoarse voice for some time. Examination reveals that the patient has cancer. A laryngectomy is performed, postoperative voice training is instituted, the patient learns to speak, and finally, he returns to his former job.

Records. After the movie, the speech pathologist plays records of the voices of esophageal-speaking patients, and then discusses the following points: (1) laryngectomy removes only the larynx, one part only of the normal speech-making equipment that includes the teeth, tongue, lips, cheeks, soft palate, pharynx, and larynx. When the larynx is removed, all that is needed is a new source for making sound. (2) The new source for making sound can be developed by forcing air into the top of the esophagus and immediately belching it. (This is demonstrated.) (3) Learning esophageal speech postoperatively is facilitated if the patient can practice the technic—swallowing air and belching it—before operation. (4) After the larynx has been removed, the patient is eligible for membership in the International Association of Laryngectomees, the local branch of which is the Cleveland Lost Chord Club.

Booklet. When the patient is admitted to the hospital, he is given a booklet entitled, *Some Helpful Information to Speed Recovery after Your Laryngectomy,** in which is explained the routine of the operation, the convalescence, the hospital stay, and rehabilitation, as follows:

This booklet is intended to help you and your family understand what we do before the operation that will remove your larynx, and how it will be possible for you to talk after the operation. Former patients have told us that this explanation gave them greater confidence in the success of the operation, and reassured them that removal of the larynx is not so severe a handicap after all.

First, there are three important questions that patients ask us, and we shall answer them here. The questions are:

1. Is this a serious operation?
2. Will I be able to talk again?
3. Will I be able to work again?

1. "Is this a serious operation?" The answer is: "Yes, but not more serious than other major operations." The operation has been performed on so many people that we know what preparation to make in advance; and the modern technics of surgery make laryngectomy generally a safe operation—and the patient usually makes a smooth recovery. There are more than 3000 "laryngectomees" (persons who have been laryngectomized) in this country. Many of the laryngectomees belong to Laryngectomee Clubs, here in the United States and in Canada; you will learn more about them a little later on in this booklet.

2. "Will I be able to talk again?" The answer is "Yes! either by means of 'esophageal speech' or by means of the artificial larynx." The talking will not be the same as before, but you will be able to speak. At a recent meeting of the International Association of Laryngectomees, most of the speakers used esophageal speech. Many of them talked so naturally that they sounded quite like normal speakers. Occasionally, a person does not, or cannot, acquire the esophageal speech, but he still can talk by using the artificial larynx. Instructions will be given to you in this booklet, in order to insure your success in talking after the operation.

**Copies of the booklet may be obtained by sending requests to the author.*

3. "Will I be able to work again?" The answer is: "Our records show that most patients who have been employed go back to the same jobs." Laryngectomees engage in all occupations and professions; there are plumbers, lawyers, employees in retail and wholesale stores, company executives, salesmen, school teachers, physicians, bookkeepers, garage mechanics, farmers. A recent study reported that 80 per cent of the men and women kept their old jobs. Some of those who changed jobs had not learned to talk. The chances of keeping the same job are much better if one learns to talk. It commonly is said that the only activity a laryngectomee cannot do—or rather should not do—is to swim. Yet, although the larynx helps a person to hold his breath, many a laryngectomee has made adequate adjustment to his job of heavy lifting in the steel mill.

Before the operation. Have you seen the motion picture called "New Voices"? In this film, there appear persons who have lost the larynx and who learned to talk again by means of esophageal speech. Your normal speech-making equipment includes your mouth—lips, teeth, tongue—your cheeks, your hard and soft palates, your nasal passages and your larynx. A laryngectomy removes only the larynx—or the normal sound-making equipment, but it still is possible to form sounds by using the esophagus—for esophageal speech.

Esophageal speech requires you to swallow air and immediately return it to your throat and mouth as a formed sound. In other words, if you can swallow air and return it to your throat and mouth, you can learn to talk after laryngectomy. You might practice this new way of swallowing and returning air as much as you can before the operation.

As to the hospital procedures, before the operation, there are a few things you and your family will want to know about. Shortly before surgery, a feeding tube will be inserted into your throat and will remain there throughout surgery and after the operation until the tissues are well healed.

After the operation. Immediately after the operation and during the next few days until the tissues are well healed, you will be fed nourishing liquids through the feeding tube. (Usually about the fifth to the seventh day after the operation, the surgeon will decide that the feeding tube may be removed and that you are ready to swallow liquids and foods normally.)

You now have an opening in your neck, and a silver tube is placed in it. You breathe through this tube. Your trachea (windpipe) receives the air you breathe directly—instead of from the nose that ordinarily warms and strains the air. For the first few days, mucus accumulates in your windpipe, and this mucus has to be removed by the nurse. At first the nurse uses the aspirator to remove the mucus for you—but shortly you are able to do this for yourself whenever you wish to.

You will learn a new way to cough. At first it will seem to be less effective, until you learn how to use your breathing muscles for coughing. The medical personnel will help you to learn this different method of coughing.

The nurses, the doctors, and the entire staff are interested in helping you to recover as rapidly as possible. They will do everything they can to make you comfortable.

On the day after the operation, you may sit up or stand up. On the third day, you may be walking about your room and helping to care for yourself. About the fifth day, the surgeon asks you to swallow so that he may check on your progress in healing. He may ask you to practice swallowing many times during the day. On the sixth or seventh day, the sutures, or surgical stitches, may be removed and you then are asked to swallow sips of water. If everything is satisfactory, the feeding tube is removed and you are given a soft diet.

Now you have reached an extremely important step in your recovery. If you can swallow, you can begin your preliminary exercises to start speech. About an hour after every meal you should practice swallowing air and belching it. The speech teacher will show you how it is done. You swallow air and immediately contract your abdomen to push the air into your throat. You use the sound made by the belch to say the vowels, such as **oh, ah.** In addition to the vowels, certain other sounds are voiced, such as **b, d, v, g, l,** and **r.** The other consonants* take care of themselves. From this time on, your progress toward adequate speech depends upon the amount of practicing you do. Occasionally, a patient is delayed from talking because

**For example: To say two, you place the tongue for t, shape the lips for oo, and then belch.*

of problems that have confronted the surgeon. The speech teacher sees you frequently to correct any faults you have acquired. Each day brings improvement and you have the wonderful satisfaction of knowing that you are going to talk again.

We already have mentioned the International Association of Laryngectomees. The Association is organized into local clubs in order that you and others may be encouraged and inspired personally by those who have made this readjustment to removal of the larynx. Members of the local club, the Cleveland Lost Chord Club, will be coming to visit you and your relatives, and they gladly will demonstrate their speech. Their experiences will help you to understand and overcome the problems you are facing. The members will invite you to visit the local club. If you live outside of the Cleveland area, you will be given the name of the club that is closest to you. Perhaps you will want to form a club in your hometown. Perhaps your experience will inspire you to join the International Association of Laryngectomees so that you yourself may help to encourage others.

The staff of the Cleveland Clinic will make all of the facilities of the hospital available to you, to insure your comfort and rapid recovery.

Best wishes to you!

Visits from esophageal-speaking patients. At some time during the patient's hospitalization, he is visited by several laryngectomees who are members of the local Lost Chord Club. These people, who have surmounted the obstacles that the patient now faces, inspire him by demonstrating how the loss of the natural voice can be redeemed by esophageal speech.

CASE REPORTS

The following case reports illustrate the value of these aids in the rehabilitation of laryngectomized patients.

Case 1. Three days before total laryngectomy, a 54-year-old white man was shown how to swallow air and belch for esophageal speech. On the third day after the operation he was walking about his room, and on the eleventh day he was given his first speech lesson. Since he had practiced the technic before the operation, it was easy for him to begin shaping his lips for vowels. Within the first half-hour, he learned to count to ten and to say, "Hello" and "How are you?" with low volume but good intelligibility. One week later, he reported that he had answered "Yes" and "No" over the telephone and had counted up to 30 without resting. One week later, he was doing words of two syllables on a single belch, and he demonstrated his speech to a prospective laryngectomee at the hospital. A week later, about a month postoperatively, he was speaking in complete sentences. Instruction was then given on inflection and phrasing. Two weeks later, about 6½ weeks after operation, he had returned to his job as foreman of a line construction crew.

Case 2. A 75-year-old white man was seen for a regular check-up in May 1954. He had a history of diabetes and impaired hearing. Seven years preceding examination, he had undergone removal of the right vocal cord, ventricle and ventricular band; biopsy had revealed epidermoid carcinoma. At examination, recurrence of the cancer was detected on the left vocal cord; biopsy showed squamous cell neoplasm. Despite his advanced age, the patient was considered by the hospital staff as a good surgical risk. However, because of his age and other physical problems, he was offered a choice between total laryngectomy and radiation. He was shown the film *New Voices*, and was given a demonstration of esophageal speech. He chose total laryngectomy. He readily learned to swallow air and belch. After the operation, three esophageal-speakers visited him. Thirteen days after surgery, he received his first speech lesson. He acquired a fair

swallow-belch and was sent home to practice. One week later, he was able to say the vowels and was shown the technic of placing his articulators for the consonants before the vowel was produced. One week later, the patient was able to swallow and belch at will. He was instructed not to whisper but to take time to complete his sentences by voice. One week later, the patient was answering questions spontaneously and could say the alphabet without resting. Two months after operation, the patient was talking spontaneously. Unnecessary facial grimaces during speech were called to his attention, and practice before a mirror helped to eliminate them.

Case 3. A 67-year-old white man who had retired from active work but who lived on his farm, was seen because of hoarseness of two months' duration with a more recent onset of dysphagia and loss of phonation. He was found to have squamous cell carcinoma that involved 85 per cent of the epiglottis, extended to the false vocal folds and to the median commissure. He was shown the motion picture *New Voices*, and esophageal speech was demonstrated. The patient quickly learned the swallow-belch. On the seventh day after surgery, he was given his first speech lesson. Within a half-hour he said five vowels, could count to ten, and say: "How are you?" "Fine," and "Thank you." Two days later, he responded spontaneously with two-word answers. His volume was low but adequate for a start; however, he tried to talk so fast that his vowels and consonants were slurred or were omitted. He was advised to be more deliberate in his speech and to be patient about forming and sounding the words. Four days later he still was talking in the same rapid, slurred manner. He talked faster than he could swallow air and form the belched sound into vowels. When he slowed his speech, it was intelligible. Two weeks later, he returned and was using the whisper, and displayed anxiety about the lack of improvement. He was told to speak only when there was air in the esophagus. Five weeks later, he returned with the complaint that he could not talk and would have to have an electric larynx; he could no longer tolerate the bloating of his stomach from the intake of excessive amounts of air. He mentioned that his wife, who was an invalid, could not understand him. He also said that his dog could not understand his orders to get the cows. He was given the address of a distributor of an electric larynx.

This case demonstrates several points about the training program: The training program should fortify the patient against intolerance of his own slow progress, and should inspire him with the resolution to cooperate fully with instructions. The patient (Case 3) was so eager to go home that he left the hospital without receiving adequate training; and he attempted to talk as rapidly as he had prior to surgery—in complete disregard of instructions. He could obtain no help in his neighborhood because no known esophageal speakers were in his area. He had all the requisites for good speech but his anxiety and impatience overcame good judgment. More frequent training periods and more detailed information about his home problems probably would have been of great help in teaching him esophageal speech.

Case 4. A 43-year-old Negro man who appeared to be in excellent physical condition, was seen because of hoarseness that had become progressively more severe over a period of months. Biopsy revealed squamous cell carcinoma on the right vocal cord, that extended beyond the commissure to the left vocal cord. The patient and his wife were shown the motion picture *New Voices*, and esophageal speech was demonstrated. He practiced and developed excellent coordination of the swallow-belch technic. After the operation he received visits from several esophageal speakers. On the third day, he was using the aspirator, was feeding himself through the tube, and was grumbling about not getting enough to eat. Eleven days after operation, he received his first speech lesson. He could belch several times in succession and said four vowels. The patient was optimistic and free from worry. Two days later, he spoke spontaneously "Yes" and "No," and

several three-word phrases. At the end of an hour of practice, he said a 16-word sentence without hesitating, and then threw his scratch pad away. Five days later, he was using three- and four-syllable words in one belch. He was having digestive problems because of intake of too much air and was advised to take smaller swallows. Six weeks after the operation the surgeon gave him clearance for returning to work.

SUMMARY

The rehabilitation program for laryngectomized patients is discussed, and four case reports are presented to illustrate the particular values of certain phases of that program.

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HYPERTROPHIC PYLORIC STENOSIS IN THE ADULT

Discussion of Etiology and Report of a Case

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AN ADULT FORM of hypertrophic pyloric stenosis has been recognized since 1835, when Jean Cruveilhier[1] first reported the case of a 72-year-old woman who presented a lifelong history of dyspepsia and vomiting. Although this disease has received far less attention than its more common pediatric counterpart, reports of cases have continued to appear sporadically since that time. Few authors have failed to express themselves on the fundamental issue of whether the disease entity is congenital or acquired. This report has been prepared not only in order to add one more case to the literature, but also in the hope that a summation of available data may provide sufficient information reasonably to resolve this central problem of etiology.

Historical Review

In 1885, Maier[2] described 35 cases discovered at autopsy. Judd and Thompson[3] in 1933 reported 20 cases confirmed at laparotomy during a ten-year period. In 11 of these the diagnosis was confirmed histologically. In the same year, Kirklin and Harris[4] reported 81 cases in which they believed that a roentgenographic diagnosis of the disease entity had been established; in 31 of their patients there was no other gastrointestinal abnormality. However, their contention that the roentgenographic finding of a crescentic indentation of the duodenal bulb with prepyloric narrowing was pathognomonic was not supported by the findings of Bockus[5] and other observers, and is not widely accepted today. Other authors whose contributions were concerned with smaller series of five cases or less include McClure,[6] Crohn,[7] Katz,[8] Wakefield,[9] Berk and Dunlap,[10] and Greenfield.[11]

Clinical Picture

Incidence. From available data, it is clear that approximately 80 per cent of the patients are males (as in the infantile type), and that there is a very wide age distribution.

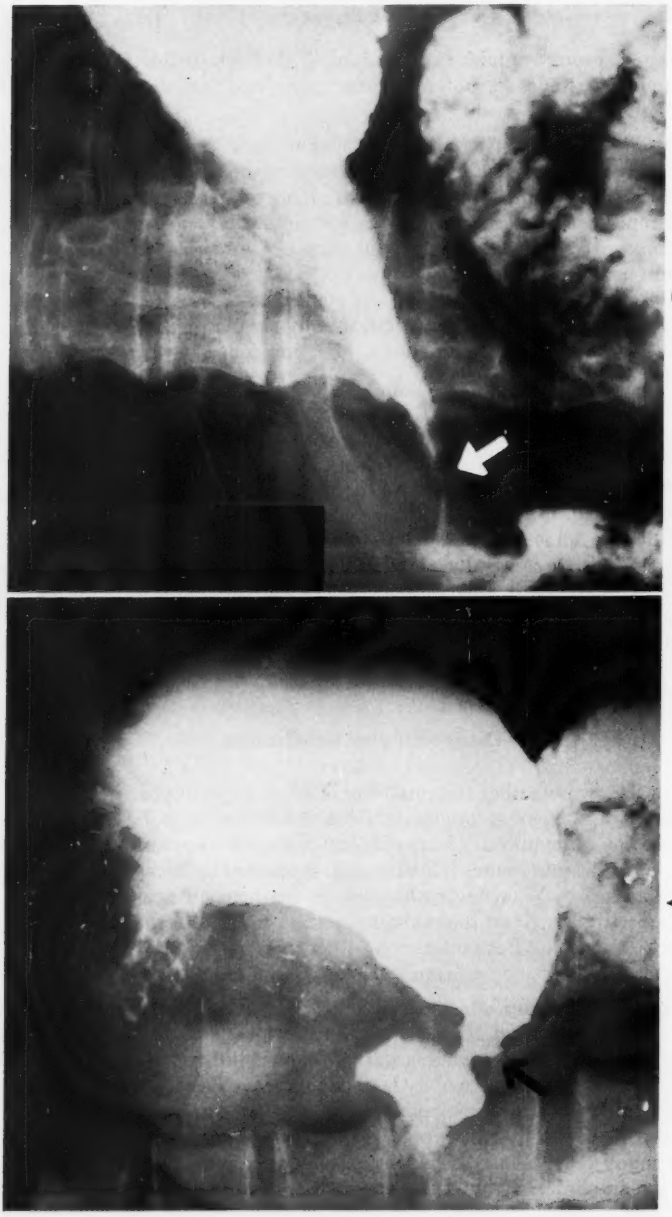
Symptom complex. No consistent symptomatic pattern of the disease emerges from the literature. The lack of histopathologic criteria contributes to the confusion, for some reported cases are inadequately described and others may well represent changes secondary to gastric or duodenal ulcerations. Judd and Thompson[3] report an average duration of symptoms of ten years, and clinical histories characterized by repeated bouts of vomiting and epigastric discomfort are not uncommon. However, confirmed cases with presenting complaints of less than one year's duration, usually simulating those of ulcer or of neoplasm, are also not exceptional. A high incidence of coexistent ulcer or gastritis is generally reported.

It is clear that the principal hypertrophy, as in the childhood variety, is limited to the circular (constrictor) muscle with little change in the longitudinal (dilator) fibers. Although Horwitz, Alvarez, and Ascanio[12] have found that in their series the thickness of the normal pyloric musculature varied from 3.8 to 8.5 mm. (5.8 $\pm$ 0.1 mm. average), criteria for the establishment of the diagnosis of adult hypertrophic pyloric stenosis remain more clinical than arithmetic. This is true both because there have been relatively few surgical specimens available for study, and also because, as Horton[13] points out, the dimensions of the pyloric musculature vary widely with the age and with the weight of the patient and also with the state of contraction or relaxation of the muscle at the time of fixation for sectioning.

Discussion and Conclusions

It is not known whether the condition of adult hypertrophic pyloric stenosis is uniformly of congenital origin, as Crohn[7] believes it to be, or whether it sometimes may be acquired. The possible etiologic role of pyloric spasm, perhaps secondary to other gastrointestinal disease, is supported by Berk,[10] and McClure,[6] but is questioned by Wakefield[9] who cites the frequency of spasm and the rarity of true hypertrophy. Katz[8] raises the interesting possibility that hypertrophy of the pylorus, may result from dilatation rather than constriction and, if acquired, might be secondary to some disturbance of the autonomic nervous system.

We believe it is justifiable tentatively to conclude that true hypertrophic pyloric stenosis in the adult is of congenital origin for the following reasons: 1. A history of gastric complaints dating from childhood is usual. 2. Pyloric spasm is common but hypertrophy is uncommon. 3. The sex incidence and the pathologic changes of hypertrophy of the circular muscle are similar in the infant and in the adult. It is probable that the disease can exist in subclinical form for many years before gastric distention or symptoms of gastritis or gastric ulcer result in clinical symptoms. Indeed, it is of interest to speculate whether



B

A

Fig. 1. (A) Preoperative roentgenogram of stomach, (B) showing prepyloric narrowing.

the presence of some degree of hypertrophy of the pyloric muscle in gastric (but not in duodenal) ulcer[12] may indicate that such hypertrophy plays a role in the pathogenesis of some gastric ulcers.

If the clinician becomes more aware of hypertrophic pyloric stenosis as a diagnostic possibility, the disease will be suspected preoperatively more often than is now the case. However, surgical exploration remains the chief means of diagnosis. At laparotomy, partial gastric resection, with its present low mortality rate, is usually the treatment of choice, for even at operation it is not possible to distinguish with certainty between hypertrophic pyloric stenosis and prepyloric malignant disease or ulcer.

Case Report

A 65-year-old white man was admitted in June 1953 with the chief complaint of six episodes of epigastric and right upper quadrant pain during the preceding year. The attacks characteristically began early in the morning, awakening him from sleep, and were associated with flatulence and vomiting; they usually lasted more than 24 hours. The most recent attack had occurred five weeks previously. He had experienced vague epigastric distress and bloating for many years, although otherwise his health had been good. There had been no loss of weight.

Physical and laboratory findings. Physical examination revealed a moderately obese elderly man (height 63½ inches, weight 151 pounds). The remainder of the examination was essentially within normal limits. The pertinent roentgenographic findings included nonfunction of the gallbladder following double-dose technic, diverticulosis of the lower descending and sigmoid colon, and an upper gastrointestinal examination that was reported as follows:

> The esophagus and proximal three fourths of the stomach are normal. There is narrowing and irregularity of the distal antrum with partial destruction of its mucosal pattern and a very small projection of barium on the greater curvature aspect probably representing an ulcer. Changes are highly suggestive of ulcerated carcinoma of the antrum. The duodenal bulb is normal. Impression: Probable ulcerated neoplasm, distal antrum. (Fig. 1A and B)

A gastric analysis revealed 12 units of free acid and 44 units of total acid after histamine stimulation. The blood hemoglobin was 14.9 Gm. per hundred ml., and a single stool examination showed no occult blood.

The preoperative diagnoses were: 1) cholelithiasis with biliary colic and 2) possible gastric malignancy. At operation on July 6, 1953, a cholecystectomy was performed for a thickened gallbladder containing four stones. An operative cholangiogram revealed a normal biliary ductal system. There was marked hypertrophy of the pyloric musculature with induration but no palpable ulcer crater. A clinical diagnosis of probable healed or healing gastric ulcer was made and a 60 per cent gastric resection with Billroth I gastroduodenostomy was performed.

Pathologic findings. The pathologic description of the resected segment of stomach was as follows:

> *Gross examination:* (See Fig. 2) The segment of stomach measured 14.5 cm. on the greater curvature, 7.0 cm. on the lesser curvature; and 11.5 cm. in circumference at the proximal line of dissection and 5.0 cm. at the distal

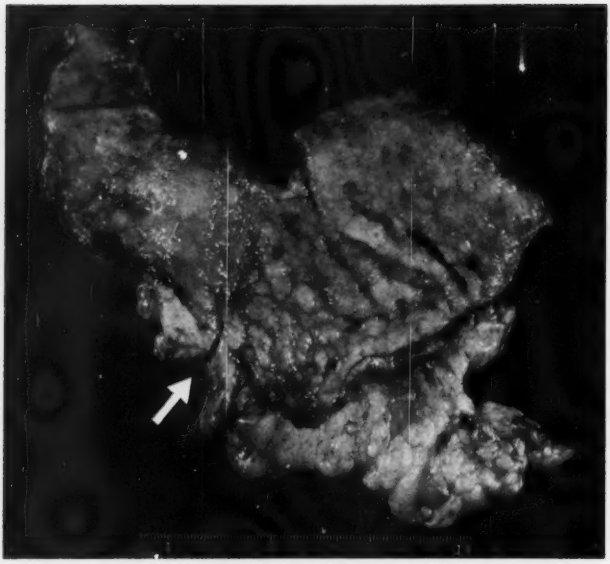


Fig. 2. The opened specimen showing marked thickening at the pyloric ring where the arrow points.

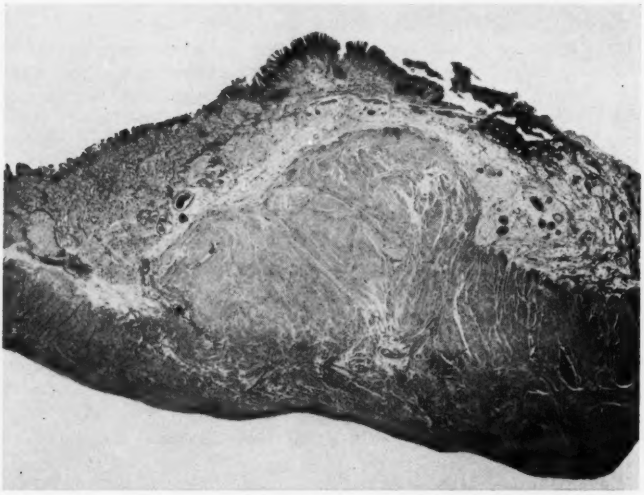


Fig. 3. Low-power photomicrograph showing muscular hypertrophy of the pylorus, principally the circular layer. X5.

line. The serosal surface was normal. There was a firm, indefinitely outlined mass palpable on the anterior wall in the pyloric region. When opened, it was found to be a zone of thickening of the pylorus, 1.3 cm. in maximum thickness and 2.0 cm. in length. On section, the tissue was pinkish gray, glistening, and had a bulging cut surface. Posteriorly, there was only slight thickening of the pyloric muscle. No scarring was apparent. Grossly, the gastric mucous membrane was not remarkable; the gastric wall was thickened to .7 cm.

Microscopic examination: (See Fig. 3) In the area of pyloric thickening, the circular muscular layer was increased in width; the arrangement of cells was of usual pattern. Nerves and ganglia were prominent. The mucosa of the stomach was of typical architecture but there were frequent plasma cells, lymphocytes, neutrophils, and eosinophils in the tunica propria. The muscularis mucosa was somewhat thickened and the muscularis, principally the circular layer, was markedly increased in thickness.

Pathologic diagnosis: Hypertrophy of the pylorus and of the gastric musculature; chronic gastritis.

Subsequent course. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day. Roentgenograms showed normal emptying

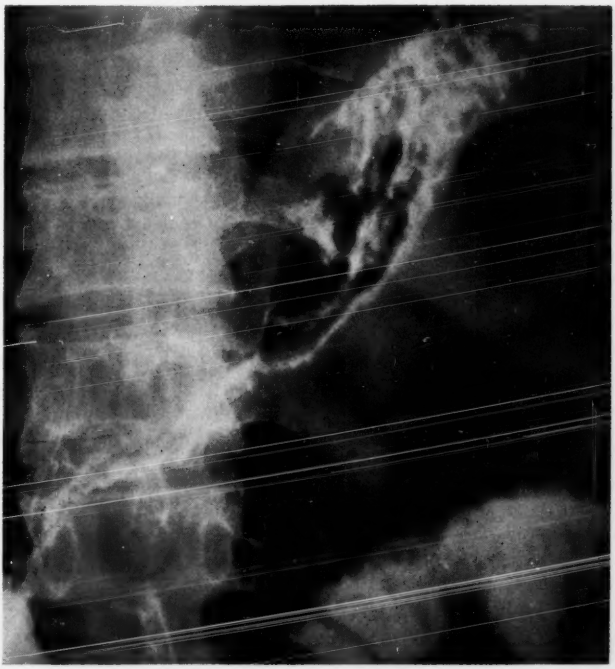


Fig. 4. Postoperative appearance of stomach by roentgenogram. About three fifths of the stomach was resected; continuity was re-established by a Billroth I anastomosis.

of the stomach (Fig. 4). Eighteen months later there had been no recurrence of the abdominal pain. His weight had remained essentially unchanged.

SUMMARY

1. The literature concerning hypertrophic pyloric stenosis in the adult has been briefly reviewed.

2. The variable clinical and histologic picture has been described.

3. It has been argued, on the basis of (1) the frequent presence of a history of epigastric distress dating to childhood, (2) the relative rarity of pyloric hypertrophy as compared with pyloric spasm, and (3) the similar sex incidence in infantile and adult hypertrophic pyloric stenosis, that a congenital etiology is most probable.

4. Because of the virtual impossibility of making the differential diagnosis between hypertrophic pyloric stenosis and prepyloric malignant disease prior to tissue section, subtotal gastric resection is the procedure recommended.

5. A single case report has been added to the literature.

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BLOOD PRESSURE REDUCTION AS AN AID TO RENAL ANGIOGRAPHY IN HYPERTENSIVE PATIENTS

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RENAL ANGIOGRAPHY is becoming an important technic in the diagnosis of hypertension of renal origin.[1] However, satisfactory renal angiograms often are difficult to achieve in the presence of arterial hypertension. At high intra-aortic pressures, the injected contrast medium is diverted from the orifices of the renal arteries into the central aortic stream. This is primarily because high arterial pressure resists satisfactory occlusion of the iliac arteries by external compression, so that the medium does not pool in the aorta and disperse laterally. The resultant inadequacies in visualization cannot be safely overcome by the use of large doses of medium, since the possible nephrotoxic effects of contrast media[2] are feared in patients with pre-existing renal disease, such as is common in hypertensive patients. However, temporary reduction of blood pressure with vasodepressor drugs permits satisfactory lateral streaming and facilitates iliac compression, so that adequate renal angiograms can be obtained with small volumes of injected medium. The present report describes the application of this principle in two cases.

TRANSLUMBAR AORTOGRAPHY AS USED FOR RENAL ANGIOGRAPHY[3,4]

The patient is given premedication to allay apprehension and discomfort and is placed prone on the roentgenographic table. A narrow, thick pad is placed under the lower abdomen for compression of the iliac arteries; a wide strap is then drawn snugly over the lumbosacral area. Novocain is injected into the area below the left twelfth rib and just lateral to the sacrospinalis muscle. The special aortogram needle is inserted into the aorta in the vicinity of the renal arteries. With the patient holding his breath (this is especially important because of the prolonged film exposure), a preliminary film is made while a small quantity of dilute medium is being rapidly injected. If the test film indicates that the needle is in a satisfactory position, 10 cc. of concentrated medium is injected as the exposure is made. Then abdominal compression immediately is released. The quantity of concentrated solution injected usually is only 10 cc. and seldom is more than 20 cc. Such volumes are considerably less than the amounts that are known to produce renal damage. We have used 70 per cent

This study was accomplished with the cooperation of Drs. Harriet Dustan, A. C. Corcoran, and I. H. Page of the Research Division, and Dr. David C. Humphrey of the Department of Cardiovascular Disease.

Urokon* as the contrast medium, but we are now testing 50 per cent Hypaque**; the roentgenographic visualization provided by each medium is comparable. However, Hypaque when used for intravenous urography has resulted in a much lower incidence of side reactions than has any other agent previously utilized.[5] Thus far, in contrast to Urokon, it has caused no unpleasant sensations in patients undergoing aortography under local anesthesia.

Modification of Technic in Hypertensive Patients

Various vasodepressor agents have been utilized to reduce the blood pressure. Angiography may be done while the blood pressure is controlled by chronic oral administration of Apresoline† or Ansolysen††. The effects of each of these drugs are prolonged and the aortogram can be made without supplemental medication or close observations of the blood pressure, in those patients who respond by decreases of pressure to nearly normal levels.

Intravenous infusions of sodium nitroprusside[6] or Arfonad§ Camphorsulfonate are effective means of temporarily reducing the blood pressure in patients who are not under chronic treatment with oral vasodepressor drugs or who do not respond to such treatment. Dilute solutions (Arfonad, 1 mg./ml.; sodium nitroprusside, 200 micrograms/ml.) are prepared. The rates of administration are adjusted to the individual requirements of each patient as determined by close observation and frequent determinations of blood pressure. The advantage of the infusion method is that the blood pressure can be reduced to a desired normotensive level; however, a person experienced in the use of these agents must supervise their administration. The effects of Arfonad or sodium nitroprusside are rapidly dissipated as soon as the infusion has been discontinued.

CASE REPORTS

Case 1. In 1950, a 40-year-old woman began to have symptoms of scleroderma involving chiefly the upper extremities. Treatment was begun in 1952 with isonicotinic acid hydrazide, and her condition gradually improved.

Blood pressure readings in June 1953 and in August 1953 were 110/70 and 140/90 mm. Hg, respectively. In June 1954, four years after initial examination, she was seen again because of failing vision and headaches. The blood pressure was 250/130 mm. Hg. The eye grounds revealed sclerosis, constriction of the retinal arteries with hemorrhages, exudates, and papilledema. Administration of Ansolysen was begun in July 1954; the blood pressure was reduced to 160/90 mm. Hg and the eye grounds improved.

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* *Urokon sodium, Mallinckrodt Chemical Works, St. Louis, Missouri.*

** *Hypaque sodium, Winthrop-Stearns, Inc., New York, New York.*

† *Apresoline, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.*

†† *Ansolysen, Wyeth, Inc., Philadelphia, Pennsylvania.*

§ *Arfonad, Hoffman-La Roche, Inc., Nutley, New Jersey.*

Although she continued to take Ansolysen, six months after the initiation of treatment the blood pressure was 224/126 mm. Hg supine and 106/84 mm. Hg while standing. The fundi showed constriction and sclerosis, but no hemorrhages, exudates, or papilledema. Blood urea at that time was 48 mg. per 100 ml. An intravenous urogram showed diminution of renal function with poor visualization of the upper urinary tract. On retrograde pyelography the left kidney was normal but the right kidney appeared to be slightly contracted.

A translumbar aortogram was obtained on February 27, 1955, at which time she was under the influence of Ansolysen, with a resting blood pressure of 116 mm. Hg systolic. Ten cubic centimeters of contrast medium was injected into the aorta in the vicinity of the renal arteries, and showed excellent filling of these structures (Fig. 1). The vascular system of the right kidney appeared entirely normal; however, the left kidney showed tortuosity of the main branches of the renal artery. A small filling defect was present on the wall of the right renal artery close to the aorta. This was not considered sufficient to cause the hypertension.

Subsequently, vasodepressor drugs did not adequately control this patient's blood pressure, and a bilateral sympathectomy was performed. A left renal biopsy specimen

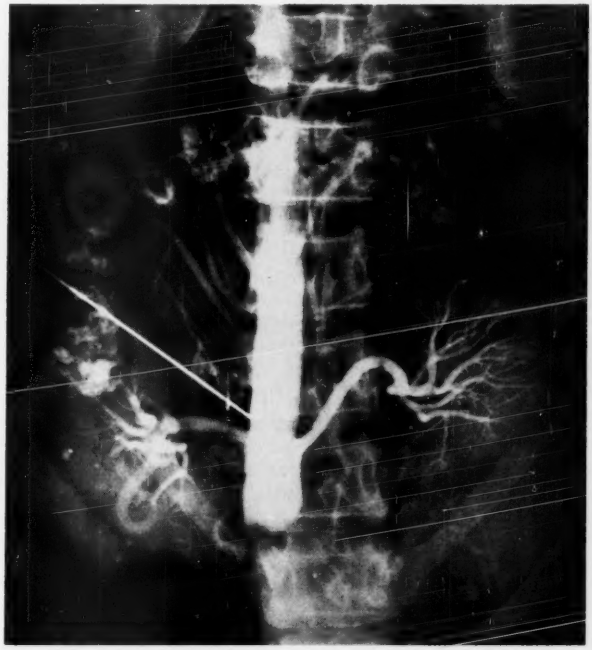

Fig. 1. (Case 1) Aortogram obtained by injection of 10 cc. of 70 per cent Urokon. The blood pressure was 116 mm. Hg systolic as a result of the administration of the vasodepressor Ansolysen. The medium is trapped in the aorta by iliac compression. Note the minor filling defect in the right renal artery close to the aorta.

was secured which showed malignant nephrosclerosis, the blood vessels revealing onion-peel changes. No necrotizing lesions or evidence of vascular changes characteristic of scleroderma was apparent in the specimen.

Comment: Renal angiography was utilized to evaluate the possibility that a renal arterial lesion might be a cause of this patient's hypertension. Under normotension, secured by Ansolysen, translumbar aortography was uneventfully accomplished. An excellent outline of renal vasculature was obtained by utilizing only 10 cc. of 70 per cent Urokon. A minor defect was shown in one renal artery but not considered significant.

Case 2. The patient was first seen in 1951 when she was 17 years of age, with a nephrotic syndrome that had been present for one year. The condition had not responded to nitrogen-mustard therapy. Subsequently, bilateral renal denervation was performed in the hope of controlling the nephrotic syndrome. At the time of denervation of the left kidney, no pulsation of the left renal artery could be palpated. Translumbar aortography was attempted at that time but could not be accomplished satisfactorily.

The nephrotic syndrome gradually disappeared during the next two years. She was readmitted to the hospital in December 1954, three years after initial examination, with a six-month history of malignant hypertension. She complained of headaches and blurring of vision. On admission the blood pressure was 240/130 mm. Hg. The fundi revealed grade III constriction and sclerosis of the retinal arteries, edema, hemorrhages, and papilledema.

The intravenous urogram showed excellent excretion of medium from both kidneys with no visible abnormalities—findings similar to those on previous urograms.

A translumbar aortogram was attempted on December 23, 1954. The blood pressure at that time was 230/120 mm. Hg. A normal right renal artery was demonstrated, but there was no visualization of the main left renal artery on two injections, although a small artery to the lower pole could be demonstrated (Fig. 2A).

For the following five weeks, vasodepressor drugs were administered; the blood pressure gradually was reduced to approximately 160/115 mm. Hg, and there was improvement of the hypertensive vascular disease. On February 1, sodium nitroprusside was intravenously administered to lower the blood pressure to levels of about 120 mm. Hg systolic, and translumbar aortography again was done. The aorta was well filled with contrast medium; both renal arteries were demonstrated clearly. There was no abnormality of the left renal artery. The aortogram also showed increased spacing of the secondary branches of the renal arteries with absence of filling of many of the smaller (interlobular and arcuate) vessels.

Comment: Translumbar aortography performed while the patient was severely hypertensive showed absence of filling of the left main renal artery. The possibility of occlusion of a renal artery as a mechanism of hypertension was considered. Aortography subsequently was done with the blood pressure reduced to nearly normal levels by intravenous sodium nitroprusside; on this occasion a normal left renal artery was demonstrated.

SUMMARY

A technic is described for conducting translumbar aortography in patients who have severe hypertension. The method involves the reduction of blood pressure to normal or nearly normal levels by the use of vasodepressor agents. This modified technic produces improved renal angiographic visualization with

A B

Fig. 2. (Case 2) A. Aortogram showing incomplete filling of the aorta, absence of left main renal artery, and an aberrant artery to lower pole of left kidney. Blood pressure was 230/120 at the time of the procedure (10 cc. of Urokon). B. Blood pressure was reduced by intravenously administered sodium nitroprusside to 120 mm. Hg systolic. Both main renal arteries and two aberrant renal arteries are demonstrated, in spite of the lower position of the needle (10 cc. of Urokon).

the use of only 10 cc. of contrast medium. Its application is described in two cases, in one of which a misleading renal angiogram was obtained when the examination was performed without reduction of blood pressure.

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NEWER THERAPEUTIC TOOLS IN CARDIOVASCULAR DISEASE

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THE most important advances in the treatment of cardiovascular disease in the last several years have been the use of the low-sodium diet in congestive heart failure, improvements in the management of acute myocardial infarction and its complications, the development of effective prophylactic measures for rheumatic fever, the use of antibiotics in the treatment and prevention of bacterial endocarditis, the surgical correction or alleviation of certain congenital cardiovascular anomalies and acquired valvular lesions, and the development of technics for aorta-iliac and segmental arterial grafting. In addition, significant progress has been made in the medical management of essential hypertension, and a number of drugs of secondary importance have been introduced for use in other cardiovascular problems. As a result, the over-all prognosis of cardiovascular disease has been greatly improved, and many patients now remain comfortable and self-supporting for considerably longer periods than heretofore.

Congestive Heart Failure

Congestive heart failure, the most common cause of death in patients who have organic heart disease, can be treated more effectively today than ever before and can be prevented from recurring for longer lengths of time. The principal factor responsible for this improvement has been the addition of the low-sodium diet to the older and well-established measures of drug therapy. Formerly, it was customary to strictly limit the fluid intake of patients suffering from cardiac decompensation and pay no attention to the amount of salt in the food. This was changed entirely about 15 years ago as a result of the demonstration that sodium retention on a renal basis is a cardinal feature of congestive failure and the most important factor responsible for water retention and the development of edema. There is uniform agreement today that the diet of patients with myocardial failure should not contain more than 500 mg. of sodium per 24 hours. Restriction of fluids is unnecessary and may even be harmful. The most satisfactory results are obtained when the patient takes between two and three liters of water daily. In persons who respond well to treatment and maintain a satisfactory state as they increase their activities, the limitation on sodium often can be lightened. Only occasionally, however, can the daily allowance be increased beyond 2000 mg.

Digitalis and the mercurial diuretics continue to be the most valuable drugs

in the treatment of congestive failure. Every patient suffering from failure should be completely digitalized, and with few exceptions the digitalized state should then be maintained permanently. Pills, tablets or capsules of standardized digitalis leaf are the preparations of choice. The purified glycosides have no special advantage over whole digitalis leaf either in clinical effectiveness or in simplicity of dosage. The best course for the physician to follow is to become thoroughly familiar with the action of one or two preparations and to confine himself to the use of those. For intravenous administration in cardiac emergencies or in the treatment of paroxysms of supra-ventricular tachycardia, Cedilanid is a safe and effective preparation. It usually is given in doses of 0.8 mg. (4 cc.) initially, followed in two to six hours by a second injection of 0.4 mg. to 0.8 mg., if necessary.

Although many persons who have cardiac decompensation will recover satisfactorily when treated only by rest, digitalis, and a low-sodium diet, the additional use of diuretic drugs hastens improvement and more promptly restores the patient to a state of comfort. Their administration, therefore, is indicated in every case. The most satisfactory preparations for routine use are the organic mercurial compounds given by intramuscular injection. Similar preparations for oral administration are available but are not as effective as those given intramuscularly. They are helpful at times, however, in prolonging the intervals between intramuscular injections in patients with chronic failure. More recently two non-mercurial oral diuretics, Diamox and Mictine, have been introduced. These are not so consistently helpful as the intramuscular mercurial preparations but are useful substitutes in persons who are unable to tolerate the latter. As with ammonium chloride, the administration of either Diamox or Mictine may reduce the need for further injections of mercurial diuretics after congestive failure has once been controlled. In addition, either preparation may at times restore the effectiveness of the mercurial drugs after the latter have ceased to cause diuresis. Diamox and Mictine owe their diuretic action to depression of sodium reabsorption by the renal tubules, Diamox by inhibition of carbonic anhydrase activity and Mictine by some as yet unexplained mechanism.

One other therapeutic aid in congestive heart failure should be mentioned, namely, the position of the patient's bed. In persons with cardiac decompensation, the recumbent position, through the effect of gravity, brings about a shift of edema fluid from the lower extremities to the upper portions of the body. This often results in prompt diminution in the edema of the lower extremities, but edema may simultaneously appear or increase over the back, and the evidence of pulmonary congestion may become more marked. Hydrothorax may develop for the first time, and the patient's condition may deteriorate rapidly. These undesirable effects of shifting interstitial fluid can be avoided by raising the head end of the bed on blocks 6 to 8 inches high. Fowler's position does not accomplish the same end.

Coronary Heart Disease

The two most important clinical manifestations of coronary heart disease are angina pectoris and acute myocardial infarction. Little progress has been made in treatment of angina pectoris. None of the surgical measures thus far designed to augment coronary blood flow have been proved to be of value. For patients who become unable to perform activities of any kind without experiencing pain, the induction of hypothyroidism by means of radioactive iodine has become the treatment of choice. Induced hypothyroidism does not, of course, alleviate the underlying coronary atherosclerosis, but it does result in a reduction in the severity and frequency of the anginal seizures in approximately 75 per cent of properly selected cases.[1] It has not been established that the patient's life is prolonged. In less severe angina pectoris, the most important single measure in treatment still consists of a detailed explanation to the patient of the cause and mechanism of his symptoms with particular emphasis on the importance of doing everything possible to avoid the attacks. Full instruction should be given regarding the various factors that often exert an important effect on the ease with which the seizures occur. These factors and the use of drugs in angina have been discussed elsewhere.[2]

Several advances have been made within recent years in the treatment of acute myocardial infarction and its complications. One of the most important of these has been the demonstration of the beneficial effect of vasoconstrictor agents in management of the shocklike state that so often occurs at or soon after the onset of the attack. There is now general agreement that a preparation of this type should be administered whenever shock develops or the arterial blood pressure falls to approximately 80 mm. of mercury. The drug most widely used is norepinephrine (Levophed) diluted in 1000 cc. of 5 per cent glucose in distilled water and administered by continuous slow intravenous drip in amounts sufficient to maintain a systolic pressure of 100 mm. of mercury or somewhat higher. Cases of mild shock usually respond promptly, and occasionally even severe shock is corrected. When vasoconstrictor preparations fail to help, intravenous administration of 250 to 500 cc. of plasma or whole blood, or the intra-arterial transfusion of whole blood may be beneficial.

Although acute left ventricular failure is a well-recognized complication of the early period of acute infarction, it has been realized only of late that milder degrees of failure are much more common than was formerly supposed. If not detected and treated, the condition may have an important effect on the mortality rate. Because of this, careful auscultation of the lung bases should be carried out twice a day during the first few days of the illness, and therapy with digitalis, diuretic drugs, and a low-sodium diet should be instituted on the first appearance of râles. In the past, far too much emphasis has been placed on theoretical objections to the use of digitalis in acute myocardial infarction. These objections have not been corroborated by clinical experience, and left ventricular failure of all degrees after infarction is now regarded as an indication for administration of the drug.

The data accumulated by the Committee on Anticoagulants of the American Heart Association[3] demonstrate that anticoagulant therapy results in an important reduction in the frequency of thromboembolic complications and in the mortality rate of acute myocardial infarction. The Committee therefore recommends the use of anticoagulants in all cases except when their employment is contraindicated by the presence of hepatic or renal insufficiency or a blood dyscrasia with hemorrhagic tendencies, or when facilities are not available for making reliable measurements of the prothrombin time of the blood. These recommendations probably are being followed today in the majority of medical centers. During the past three years, however, doubt has been expressed with increasing force about the need for anticoagulant therapy in every case of infarction. Russek and others[4] have published studies which demonstrate that treatment of this kind is not actually necessary in "good-risk" cases. The main problem now is to be certain that "good-risk" cases can be reliably identified. Until we are sure on this point, it appears best to continue the routine use of the drugs.

A period of strict rest is an essential part of the management of every case of acute myocardial infarction, but the term "strict rest" was redefined a few years ago. Levine[5] and others have demonstrated that after the period of shock is past, and in the absence of great debility or a cerebrovascular accident, the patient may safely be permitted to sit in a chair for as long each day as he desires. He should be helped in and out of bed, however, and should be allowed no other privileges except for the use of a commode at the bedside. The length of time this program is carried out before allowing him to walk again is determined by the severity of the attack. Most patients can be permitted to take a few steps to the bathroom at the end of three weeks and can be granted gradually increasing activity after six weeks. In the absence of angina pectoris and myocardial insufficiency, a return to some form of work usually is permissible at the end of three months.

Rheumatic Heart Disease and Bacterial Endocarditis

The ultimate aim of cardiovascular research is the prevention of all forms of heart disease. Although this goal is still far short of achievement, important progress has been made with respect to rheumatic heart disease and bacterial endocarditis. It has been established that most initial and recurrent attacks of rheumatic fever can be prevented by early and adequate treatment of beta hemolytic streptococcus infections. The treatment of choice is the intramuscular administration of penicillin, either in the form of a single injection of 600,000 to 900,000 units of benzathine penicillin G or as procaine penicillin with aluminum monostearate in oil, 300,000 to 600,000 units every third day for three doses.[6] Prophylactic treatment against streptococcal infections should be carried out in all persons who have a history of previous rheumatic fever or chorea or who present evidence of rheumatic heart disease. Sulfadiazine may

be given in doses of 0.5 to 1.0 Gm. each morning, or penicillin may be employed either by oral administration daily before breakfast in doses of 200,000 or 250,000 units or by the intramuscular injection of benzathine penicillin G, 1,200,000 units once a month. Treatment should be continued the year round until the patient is at least 21 years of age and possibly for life.

Although the majority of cases of bacterial endocarditis can now be treated successfully, the disease still has a mortality rate of 20 to 25 per cent because of delays in diagnosis and infections by penicillin-resistant organisms. In cases due to penicillin-sensitive organisms, treatment with penicillin alone usually suffices. Combined antibiotic therapy consisting of procaine penicillin 600,000 units every six or eight hours and streptomycin 1 Gm. daily has, however, become the treatment of choice because of the synergetic action of these two agents. Streptomycin is continued for 10 to 14 days, and penicillin for three weeks or longer. The same regimen often is effective in cases due to enterococci or other penicillin-resistant organisms. Only when penicillin and streptomycin have failed should bacteriostatic agents (aureomycin, terramycin, tetracycline, chloramphenicol and erythromycin) be used.

Bacterial endocarditis is, in most instances, a complication of rheumatic valvular disease or congenital heart disease. Many cases undoubtedly can be prevented by administering penicillin to patients with such cardiac problems before dental extractions, the removal of tonsils and adenoids, and obstetrical delivery. A suitable schedule consists of 600,000 units of procaine penicillin and 600,000 units of procaine penicillin with aluminum monostearate in oil administered intramuscularly approximately one hour before the operative procedure.[6] Patients who are sensitive to penicillin and those who are undergoing surgery of the urinary or lower gastrointestinal tract should be given one of the broad spectrum bacteriostatic preparations in full dosage for five days beginning the day before the surgical procedure.

Essential Hypertension

A number of effective and fairly dependable hypotensive drugs have become available within the past few years. These preparations do not correct the underlying cause or causes of hypertension, but they reduce blood pressure in many patients and by so doing control symptoms and probably prolong life. It is fair to say that the outlook for the hypertensive person is better today than at any time in the past. Rauwolfia serpentina is the most widely applicable of the newer preparations, and, in our opinion, should be the first agent employed in the treatment of all cases except those of severe degree or in the malignant phase. The drug acts by a central tranquilizing action, and undesired side effects are infrequent and harmless. It is given in the form of the crude root (100 to 200 mg. daily), the alkaloid reserpine (0.25 to 2 mg. per day), or the total alkaloidal (alseroxylon) fraction (2 to 8 mg. daily). Because of its slow action, a decision as to its helpfulness in a given case should be postponed until after a trial of six weeks. If Rauwolfia alone proves ineffective, it may be given in combination

with phenoxybenzamine and protoveratrine (Mio-pressin). When this fails, pentolinium tartrate (Ansolysen) generally is the next preparation employed. It may be administered alone or with Rauwolfia and has largely replaced hexamethonium and Apresoline. Sympathectomy is now employed only in cases that have entered the malignant phase and fail to respond to any form of drug therapy.

Cardiovascular Surgery

The value of commissurotomy for mitral stenosis has been established by extensive experience in all parts of the country. To date, 165 patients have been operated on at the Cleveland Clinic with a mortality rate of 4 per cent. Operation is not necessary in patients who have had no symptoms, nor is it advisable in patients who have significant aortic valvular disease or more than slight mitral insufficiency. Intractable congestive failure usually, but not always, is regarded as a contraindication. With these exceptions, and in the absence of active rheumatic carditis or bacterial endocarditis, commissurotomy is now recommended for all patients with mitral stenosis. The technic of commissurotomy for aortic stenosis also has been sufficiently developed that the operation should be advised in all cases of high-grade obstruction producing symptoms in persons less then 50 years of age.

Space does not permit a detailed discussion of the surgical treatment of congenital cardiovascular anomalies. The most common anomaly that can be completely corrected is a patent ductus arteriosus. In adults the recognition of this condition seldom is difficult, but in young children and especially in infants, the characteristic continuous, "machinery-type" murmur often is absent. In such patients a precise diagnosis can be established only by cardiac catheterization. Until recently this procedure was considered hazardous in infants and small children, but Dr. F. Mason Sones of our group has clearly demonstrated that such is not the case. He has performed catheterization in 108 children younger than 18 months of age, including 6 under the age of one month. All had congenital defects of such severity that survival for more than six months did not seem a reasonable expectation. Twenty-seven of the children were found to have anomalies that could be cured or corrected by surgery. Thirteen had a patent ductus arteriosus with only a nonspecific systolic murmur. Surgical division was performed in each case, and there was only one postoperative fatality. The majority of children with congenital heart disease who die before the age of two years have lesions that are not amenable to surgical correction, but a certain number have curable conditions. Because of this, cardiac catheterization is recommended for all such patients, regardless of age, who are dangerously ill.

The most recent addition to the therapy of cardiovascular disease has been arterial grafting for aneurysm or segmental arteriosclerotic obstruction of the abdominal aorta and its major branches. Discrete or segmental arteriosclerosis obliterans occurs predominantly in three locations, the aortic bifurcation, the

iliac arteries, and the superficial femoral artery. The characteristic clinical manifestation of the condition is intermittent claudication with pain in the back, buttock, thigh or calf depending on the site of the obstruction. In contrast to those with the diffuse form of arteriosclerosis obliterans, the patients usually are less than 55 years of age and seldom present evidence of severe ischemia or gangrene of the toes and feet. A rough estimate of the extent of the segmental occlusion often can be made by physical examination, but accurate evaluation requires translumbar aortography and femoral arteriography. Approximately one-half of all persons who have intermittent claudication are found by such studies to have an area of obstruction which can be replaced by a graft, but this does not mean that all should be operated on. In a considerable number adequate collateral circulation will develop spontaneously with time, and most patients therefore should have a thorough trial on conservative management. Arteriosclerotic aneurysms of the abdominal aorta and iliac arteries present a different problem. Fatal rupture of the aneurysm occurs in nearly three-fourths of all cases within three years of the time of original diagnosis. Resection and grafting, therefore, should be carried out promptly in all patients except those beyond the age of 70 years and those in poor general health. Even in the latter groups, the occurrence of symptoms referable to the aneurysm should lead to immediate surgery, although the mortality rate will be considerably higher than the 5 per cent or less which attends operation in younger patients. Dr. A. W. Humphries of our group has performed aorta-iliac grafting in 70 patients with a mortality rate of 4 per cent.

In conclusion, this discussion has not by any means touched upon all of the recent additions to the treatment of cardiovascular disease. An attempt has been made, however, to mention and partially review those that appear to be most significant. Because of these advances, the prognosis of patients suffering from many forms of cardiovascular disease is better today than at any time heretofore, and the gains of the past few years justify optimism concerning the fruits of further clinical and laboratory research.

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FOREIGN BODIES OF DENTAL ORIGIN IN THE MAXILLARY SINUS

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THE following two cases are presented because of their unique nature. They demonstrate the behavior of three foreign bodies of dental origin in the maxillary sinus, each of which originated in the maxillary alveolus. In two instances the objects, which were considerably larger than the natural ostium, were extruded to the outside through the nose. Two of them were associated with secondary oral antral fistulae through tooth sockets that had healed per primum following exodontia procedures.

CASE REPORTS

Case 1. The patient, a 58-year-old woman, was first seen in June 1953. She complained of a chronic clear postnasal discharge of long duration which had always been worse in winter months. Following removal of the upper teeth six months previously, the postnasal discharge became yellow, and this was accompanied by a sensation of pressure in the right cheek.

Examination revealed excessive clear mucous discharge but no pus. Transillumination of the right antrum was dim. Radiographs of the sinuses showed uniform cloudiness of the right antrum and thickened mucosa in the left antrum. There was a large opaque foreign body within the right antrum and two smaller opaque foreign bodies in the left maxillary alveolus (Fig. 1). Irrigation of the right antrum produced a purulent return.

Dental radiographs indicated that the alveolar foreign bodies were in the left maxillary cuspid and molar areas (Fig. 2). In addition, an area of radiolucency suggestive of inflammatory change was noted in the region of the left maxillary cuspid. Exploratory operation of the left maxillary cuspid area was performed on July 29, 1953. During this procedure a semisolid green material was removed which was believed to be a zinc oxide eugenol cement. An inflammatory cyst also was found and removed. Pathologic diagnosis was dental cyst with chronic inflammation.

The patient was advised to have an antromeatal window made in the right inferior meatus for removal of the foreign body and drainage of the antral suppuration, and during the same hospitalization a maxillary alveoloplasty for correction of the alveolar contours and removal of the remaining foreign body on the left. This was deferred by the patient.

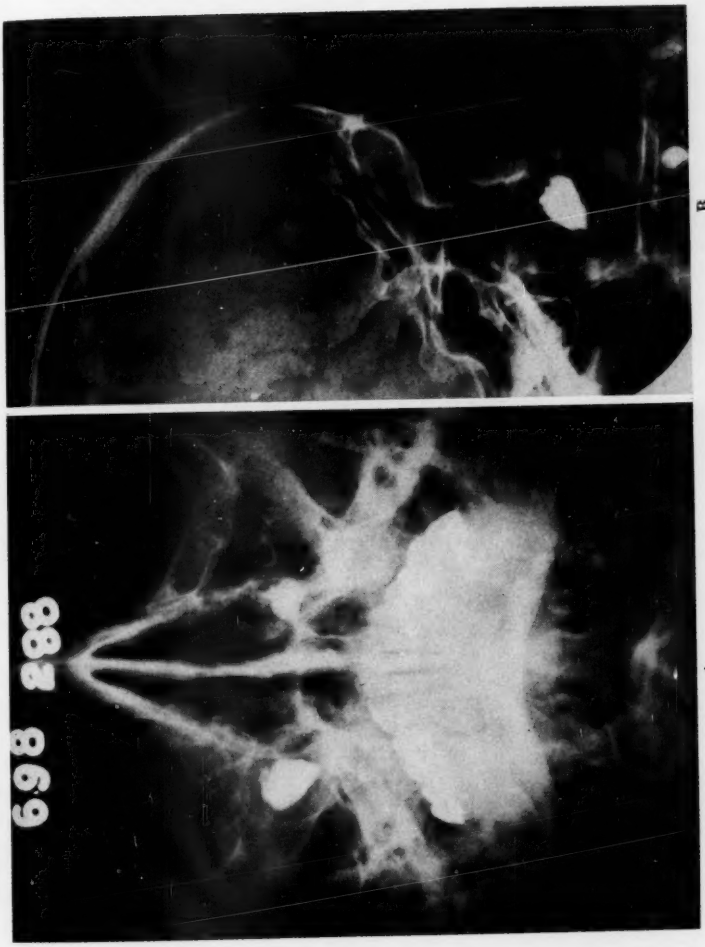

Fig. 1. (A) Waters view and (B) lateral view of sinuses demonstrating foreign bodies in the right antrum and left maxillary cuspid and molar areas. The right antrum is dark.

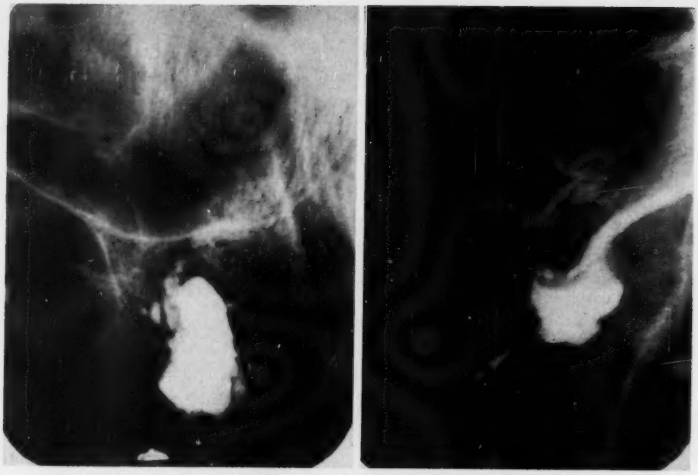

Fig. 2. Dental radiographs showing the alveolar foreign bodies in the left cuspid and molar areas.

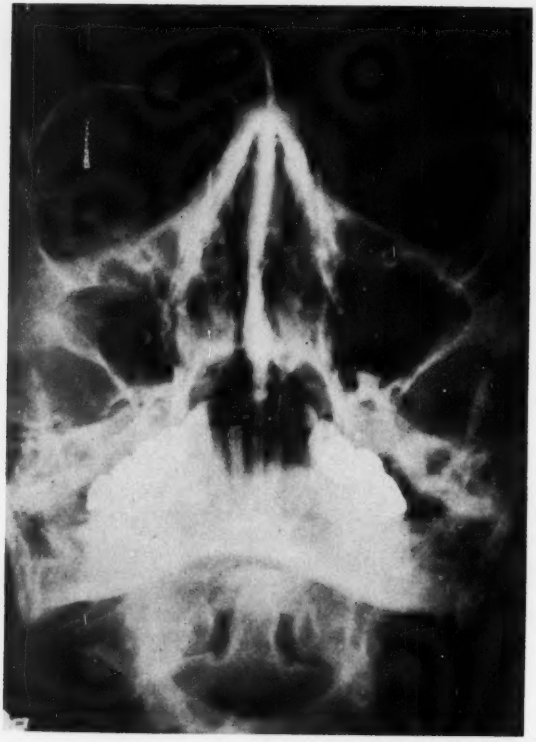

Fig. 3. Waters view showing clear right antrum after foreign body had passed postnasally. The left maxillary cuspid foreign body had been removed by dental surgery. The foreign body in the left maxillary cuspid area is now projecting into the antrum.

In February 1954, eight months after her first visit, the patient returned stating that she had had an episode of pressure and pain in the right cheek for three or four days, followed by hawking a large stony object postnasally. The symptoms were immediately relieved.

Examination at this time revealed a clean nose, clear transillumination, and clear irrigations bilaterally. Radiographs revealed that the foreign body in the right antrum was missing (expectorated), the one in the left cuspid area was gone (surgically removed), and the one formerly in the left molar area was now in the left antrum (Fig. 3). The expectorated object measured 1 by ½ by ½ cm. (Fig. 4).

Fig. 4. The foreign body that was hawked postnasally.

In March 1954, maxillary alveoloplasty was performed under general anesthesia, with immediate rebasing of the upper denture. Three weeks later an examination revealed complete and firm healing and no evidence of irritation or ulceration from the rebased denture. Operation for removal of the remaining foreign body was deferred by the patient.

Five months later, September 1954, the patient again returned, this time with a history of pain over the left cheek, purulent postnasal discharge, and an ulcer on the gum. Examination demonstrated pus in the left middle meatus and a large oral antral fistula in the region of the left maxillary first molar area about ½ cm. in diameter through which thick pus was exuding. A probe was easily passed into the antrum. Radiographs showed a cloudy left antrum with the foreign body now in the region of the natural ostium (Fig. 5). Dental radiographs taken of the first molar region demonstrated no evidence of residual alveolar foreign body. A left nasoantral window was made in the inferior meatus and the fistula closed with a flap from the buccal aspect of the alveolus and cheek.

Case 2. The patient, a 20-year-old man, was first seen in December 1954 with the following history. The upper left first molar had been extracted in June 1951. He was told by his dentist that he had a retained root fragment and was advised to consult an oral surgeon for its removal (Fig. 6). However, healing of the gingival opening was complete and the patient did not follow this advice.

In March 1952 he experienced severe localized pain over the left antrum of several days' duration. The pain was completely relieved by a bout of sneezing during which the fragment was expelled into his handkerchief (Fig. 7). Following this a fetid discharge was noted postnasally and from an ulcer at the site of the previously healed tooth socket.

Examination revealed a left middle meatus full of pus and inflammatory granulations. There was a large opening in the region of the left maxillary first molar which also was full of pus and granulations. A probe passed readily into the antrum. Treatment consisted of a left Caldwell-Luc procedure. The incision was made in such a way as to create a tongue-shaped flap that was mobilized and sutured over the fistulous opening.

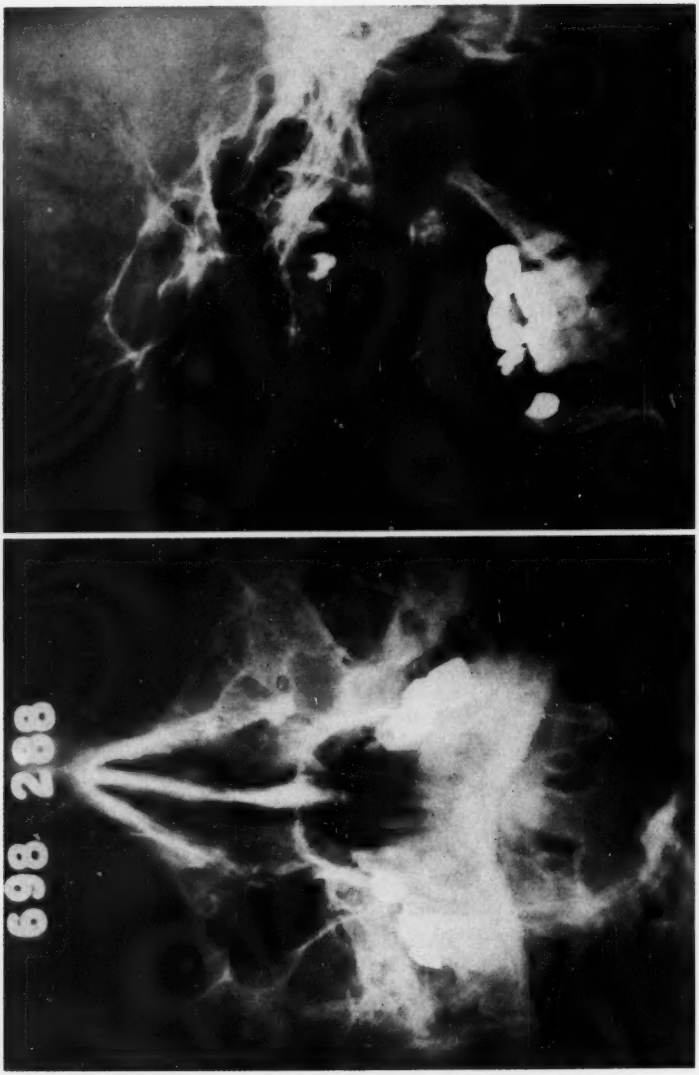

Fig. 5. (A) Waters view and (B) lateral view demonstrating cloudy left antrum with foreign body in the region of the natural ostium.

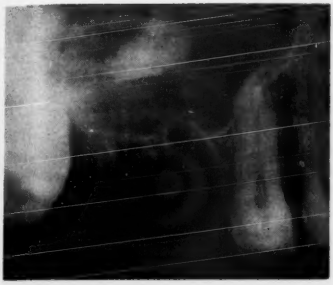

Fig. 6

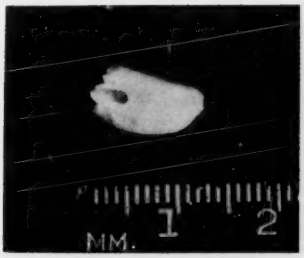

Fig. 7

Fig. 6. Dental radiograph showing root fragment in the antrum.

Fig. 7. Tooth fragment that was expelled by sneezing.

DISCUSSION

The interesting aspect of Case 1 is the pathway of the foreign bodies and the associated complications.

It seems likely that the pressure exerted upward by the denture during the act of chewing, would cause pressure atrophy of the tissue between the foreign body and the antral cavity. The presence of infection around the foreign body would aid this process. Thus a pathway would be slowly created through which the foreign body and infection were introduced into the antrum. Since the foreign body was relatively light (specific gravity 1.50), it would tend to move within the medium of pus (specific gravity 1.05) more easily than would a heavy metallic object. If, during sleep, the patient were lying in such a position that the medial wall of the antrum were down and the foreign body were in the region of the natural ostium, it is quite conceivable that the ciliary action would move the object into the ostium. According to Bowditch,[1] ciliated epithelium is capable of 7 Gm.-mm. per minute per sq. cm. of work. Movement of the above object would be well within these limits.

Once in the ostium, the partial or complete obstruction produced would cause a rising intra-sinus pressure that in turn would hold the foreign body in place. Pressure atrophy would allow it to proceed gradually into the nose and thence be expelled as occurred in the first episode in the first patient. In the second episode the increased intra-sinus pressure caused reopening of the original tooth socket, producing a fistula and relief of the pressure.

In Case 2, it is probable that the same mechanism caused the root fragment to be extruded into the nose and the tooth socket to be reopened as a fistula.

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PROBLEMS OF GIFTED CHILDREN

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and

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THE need for early identification of gifted children in our school systems is recognized but is not being met adequately. Children whose intelligence quotients are above 140 are considered gifted and they comprise approximately 1.33 per cent of all children. Gifted children often profit significantly from the challenge of additional special work. Failure to recognize their superior abilities early in their school careers and to challenge them may cause gifted children to become bored, frustrated and even to fail in school.

Emotional maladjustments may interfere with the performance of a gifted child, thus the anomalous situation of a genius who fails in school is not uncommon. The physician sometimes sees a child who has multiple complaints but in whom the findings on physical examination are normal. In such a child, psychological study may reveal the basis of the problem: the child may be gifted, his superior abilities may have gone unchallenged and unchanneled and the physical symptoms may have resulted from conversion. When the underlying problem has been thus defined, treatment must cover broad areas focusing primarily on the home and the school.

The following three case reports are presented to illustrate some of the problems of the gifted child.

CASE REPORTS

Case 1. A 7½-year-old boy was seen initially in the Department of Pediatrics because of multiple complaints including dizziness, pain in the wrists and knees, cough, and headache. The mother noted that he had been "nervous," crying easily because of seemingly minor frustrations. His school work had been poor and the teacher reported that he paid little or no attention in class. The general physical examination was negative.

Psychological evaluation revealed a quiet boy who responded very well to all commands. On the Stanford-Binet Intelligence Test, the child was found to perform at an 11½-year level, yielding an I.Q. of 153. From the child's response, it was apparent that he was bored and annoyed with his school work. He was not completing the requirements for even average second-grade work, and he had adopted various attention-gaining mechanisms in school. It appeared that the complaints of headache and dizziness had been used as an excuse to avoid attending school.

The child's social adjustment was good; he was well liked and played well with other

*Psychologist.

children. His family adjustment was only fair. The boy's father was his idol but there was little time for the father and son to be together since the father maintained a part-time job in addition to his full-time job. He did this so that the children could have the material things that he believed would bring them happiness. The father was helped to gain greater insight into the emotional factor in his son's problem, and came to realize that the toys were not nearly so important as his personal attention. With greater understanding on the part of both the family and the school, the boy is reportedly showing improved adjustment in school and has fewer physical complaints.

Case 2. An 8½-year-old boy was seen initially in the Department of Allergy. The mother wanted the child to have a general check-up because of the multiple complaints including irritability, lack of attention in school, daydreaming, and headaches. There was a strongly positive family history of allergy on the paternal side. The physical examination was not remarkable. The conclusion of the allergist was that there probably was a mild nasal allergy but that the behavior problem seemed more prominent.

Psychological evaluation revealed a restless boy who could be directed but who evidenced mild negativism. On the Stanford-Binet Intelligence Test, his mental age was 12 years 9 months, yielding an I.Q. of 150. Variability on the testing was marked, with effort being expended from year 9 to average adult levels. He did well on abstract reasoning but found greatest difficulty in reading and vocabulary comprehension. In school this boy did well sporadically when given tests, but he spent most of the time daydreaming and dawdling, seldom completing the work assigned.

Personality testing indicated the presence of some emotional immaturity and insecurity. The boy appeared to be finding great difficulty in transferring his identification from his mother to his father in a normal manner. The mother seemed to be a dominant figure and the father was described as a very stern and rigid person who found it impossible to be companionable with the boy. The parents were persons of superior intellect and they approached life with an overintellectualized, rigid attitude. They demanded strict conformity to socially acceptable behavior patterns. In a very real way this boy had not been permitted to release his energies in a childlike manner.

An attempt was made to interpret to the parents the need for greater warmth and for more companionship with the father, and the child was referred to the supervisor of special education for consideration of a more appropriate academic placement. Six months later the parents reported that with some change in his academic program he seemed to be showing greater interest in school although he still had some difficulty concentrating. They also stated that he had become more cooperative at home.

Case 3. A 7½-year-old boy was seen initially in the Department of Pediatrics. The chief complaints were stuttering, nervousness, and lack of appetite. There were no remarkable physical findings. His appetite was described as adequate in the summer but poor in the winter. It was brought out that the father was an extremely stern person with little patience, and that the child was afraid of him. The child stated in response to a question about his nervousness: "My father makes me nervous." He gave the same answer to inquiries about his poor eating and his stuttering.

Psychological evaluation revealed a very quiet child who gave the initial impression of having exceedingly poor emotional adjustment. He showed evident pleasure in the challenge of something difficult and stuttered intermittently on what seemed to be a tension basis. The Stanford-Binet Intelligence Test revealed a mental age of 11 years 10 months, yielding an I.Q. of 160. He easily verbalized his fear and his real resentment of his father. The mother had been overprotective and had in several instances prevented

opportunities for much-needed socialization. For example, she provided a taxi to take him to and from school rather than allowing him to walk with other children.

The child was not getting along well in school. He was frequently absent and the teacher believed that these absences were not always warranted. His grades on tests were good but his work habits were reported to be variable. The teacher stated that social adjustment was notably poor: He did not show interest in group activities and his classmates appeared to regard him as different from them.

Here was a child whose intellectual capacities fell within the range of genius but who was maladjusted in the emotional, social, family and academic areas. An approach taking all aspects into consideration was necessary to bring about improvement. Academically, it was recommended that he be placed in an accelerated work program; this was carried out. The teacher has noted some change in this setting of greater challenge, however it is as yet too early to determine how significant this improvement will be. It has been impossible to obtain the family's cooperation or to give them insight into the child's problems. It is likely that his accomplishments will be limited unless the members of his family become more cooperative.

SUMMARY

Three case reports are presented to illustrate the problems of the gifted child. In each of the cases, the child presented multiple complaints that were found to have no physiological basis. Intelligence tests revealed each child's superior abilities, and the physical symptoms were attributed to the conversion of emotional factors resulting from the lack of challenge in schoolwork and the lack of understanding in the home.

ARTIFICIAL HIBERNATION

Technic, and Observations on Seriously Ill Patients

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Research Division

ARTIFICIAL HIBERNATION attempts to duplicate the metabolic state of the naturally hibernating animal which during winter sleep seems to be very resistant to serious injury, including temporary arrest of the circulation, and to infection. At the approach of winter, the maple tree loses its leaves; the lizard disappears to sleep; some warm-blooded animals, like the ground hog, go into hibernation; but man, in the face of severe external conditions tries to protect the stability of his internal environment. Thus, when anything disturbs him, reactions of defense set in. The defense reactions often overcome the disturbing factor, but sometimes they mount to an impractical and futile fight.

In seriously ill patients, uncontrolled defense reactions, such as extreme rises in body temperature, immoderate secretion of epinephrine, excessive vasoconstriction, and increased metabolism may produce more damage and be much more harmful to the body than the aggression itself. In the disorganized struggle that follows, many patients die. The body's reaction may be dampened by hibernation, so that, like the hibernating animal, the patient can undergo the aggression without sustaining self-inflicted damage. This, at least, is the principle on which Laborit and Huguenard[1] have based their application of artificial hibernation.

Artificial hibernation establishes, for the time, a retrograde evolution that, in emergent situations, attempts to copy the status of creatures less evolved than man himself. Real hibernation cannot yet be duplicated. The fall of temperature in artificial hibernation is less; there is, moreover, a tendency to ventricular fibrillation at low temperatures which is unknown in natural hibernation.

The purposes of this paper are to review aspects of artificial hibernation reported in the European literature and also to describe our own experiences in cases in which we have followed the French technic.[2]

We have used this new procedure only in patients whose clinical condition was deteriorating so rapidly that, with currently available methods but without hibernation, it seemed hopeless. Our ultimate results reflect this selection; nevertheless, temporary improvement often was observed, and most of the patients were more comfortable than prior to hibernation. Our results tend to confirm those of Laborit and Huguenard, and we believe that further application in patients whose clinical condition is less critical than the ones described is now indicated.

Indications for the Use of Artificial Hibernation

Artificial hibernation has been advocated for use in general surgery in the poor-risk patient, in cardiac surgery, neurosurgery, and in obstetrics.[1] The relative value of this procedure as compared with refined anesthetic technics is hard to assess from the available reports, especially in the category of poor risks. The first reports on treatment of severe myocardial infarction in patients are favorable[3]; experimentally, dogs that would have died after ligation of a coronary artery, survived when this operation was performed under hibernation.[3] Artificial hibernation was used for prevention and treatment of wound shock during the war in Indochina.[4] Jaulmes[5] compared shock resulting from bleeding in anesthetized dogs and in dogs under hibernation; he reported that the hibernating dogs withstood bleeding better and longer. The ultimate survival of these dogs, however, was not studied.

It might be asked: Of what good is prolongation of life if, during hibernation, repair of existing damage does not take place? However, a large experience[1] indicates that wound healing proceeds unimpaired. Premature and newborn children, unable to resist the aggression of a new and hostile world, continue to grow during hibernation, notwithstanding low body temperature. Insufficient data are available to judge regeneration of higher organs such as the liver and the kidney.

Artificial hibernation also has been used in the treatment of severe infections. Leucocytosis certainly is not impaired, but rather is increased. Bacterial growth is slowed though not arrested, so that antibiotic therapy should be continued as before hibernation. Artificial hibernation has been used successfully to reduce temperature in the hyperpyrexia of hemorrhagic scarlet fever,[6] and in babies with severe infections (often in the gastrointestinal tract), a condition called "neurotoxicosis" by the French.[1]

Artificial hibernation has been advocated for serious conditions in which oxygenation is insufficient because of cardiac failure, pulmonary embolism or other impairment of the respiratory system.

From the few foregoing examples, it is evident that a large field of uses for artificial hibernation is yet to be explored.

"Neurovegetative Blockade" ("Inhibition neuro-végétative; neuro-endocrinienne")

In simple refrigeration, the patient is anesthetized and subsequently cooled. The HCO_3-content in the blood falls when no special precautions—such as overventilation—are taken.[7,8] The defense reactions of the body set in, and oxygen consumption is increased, at least in the beginning. Rather deep anesthesia is required to prevent shivering.

Conversely, in artificial hibernation, the patient is given a combination of drugs intended to dampen certain parts of the central and the autonomic

nervous systems.[1,2] The blocking is said to take place at the levels of cortex, midbrain, ganglia, and nerve endings. Moreover, the "neurovegetative endocrine" system is blocked, and reactivity to substances such as Adrenalin is said to be diminished. Thus, the constancy of the internal environment no longer is maintained. After blockade, when one leaves a patient without covering in a room of ordinary temperature, his body temperature spontaneously will go down to about 32 to 28 degrees C. (90 to 82 degrees F.). During hibernation, there is no shivering, and no increase in oxygen consumption. Laborit[1] believes that the severe, generalized vasoconstriction that occurs during the defense against aggression is injurious to the organism. Thus, he attempts to produce vasodilatation.

Drugs Used in Hibernation

To point out the importance of hibernation-drugs, Jaulmes[5] listed four procedures in descending order of their protective ability against shock by bleeding; the sequence is: (1) artificial hibernation, (2) refrigeration alone, (3) administration of chlorpromazine without refrigeration, and (4) administration of ganglion-blocking agents like hexamethonium.

The most important drugs used in artificial hibernation were all developed in France by the firm of Rhône Poulenc; they are derivatives of phenothiazine: Phenergan, Diparcol, and chlorpromazine. Huguenard[2] listed the properties of the phenothiazine derivatives and we have transposed his list into two schematic drawings (Fig. 1). Figure 1A indicates functions and nerves that are inhibited. Figure 1B indicates functions that are enhanced. Phenergan, Diparcol, and chlorpromazine have to a certain extent similar actions, although there are differences. Phenergan for example is an antihistaminic. Diparcol is supposed to be a bronchodilator and to inhibit bronchial secretion. Chlorpromazine is by far the most important of the phenothiazines in artificial hibernation.

Additional drugs are used, as will be indicated in the section on technic, with the purpose of (1) supporting the action of the phenothiazine derivatives (Demerol hydrochloride, barbiturates); (2) reducing capillary permeability (thiamine); and (3) preventing the occurrence of intravascular thrombosis, especially during the period of rewarming (heparin). Other drugs like Hydergine, $MgSO_4$ and procaine are alternated with the derivatives of phenothiazine to prevent development of tolerance. The use of growth hormone also is advocated, as it is hoped to have an anabolic effect.

I am unable to assess the relative virtues of activities of the many drugs used. One is reminded of the tailor who, when blamed for having made a mistake on an expensive coat, answered in defense: "Sir, the art of tailoring has not regressed to the state of an exact science." In other words, it seems to be intuition that has guided the French. It is an approach that is widely criticized in this country; however, I think that we should reserve our judgment in this instance until we have had more experience.

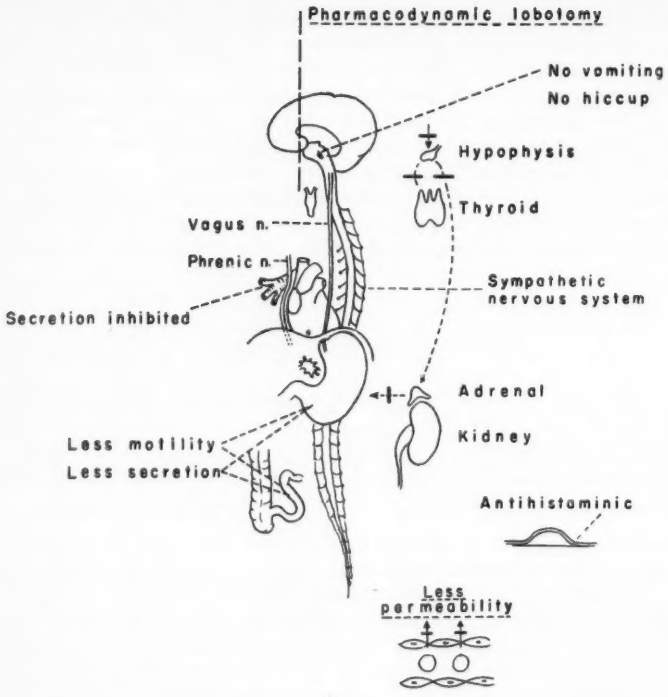


Fig. 1. Pharmacologic action of the phenothiazine derivatives: chlorpromazine, Phenergan, and Diparcol, as listed by Huguenard[2] and transposed into a diagram. (A) Functions or nerves that are inhibited.

Technic of Artificial Hibernation

The following technic of hibernation is based on that of Laborit and Huguenard.[1,2] As we instituted hibernation only as a last-resort measure in very ill patients, our procedures differed somewhat from the standard French prescription.

Outline of Technic

Pretreatment: Give 50 mg. chlorpromazine intramuscularly immediately upon decision to start hibernation.

Induction: Start intravenous infusion of 5 per cent glucose in water at a rate of about 15 drops per minute. Inject into the tube every 15 minutes, 2 cc. of the following mélange:

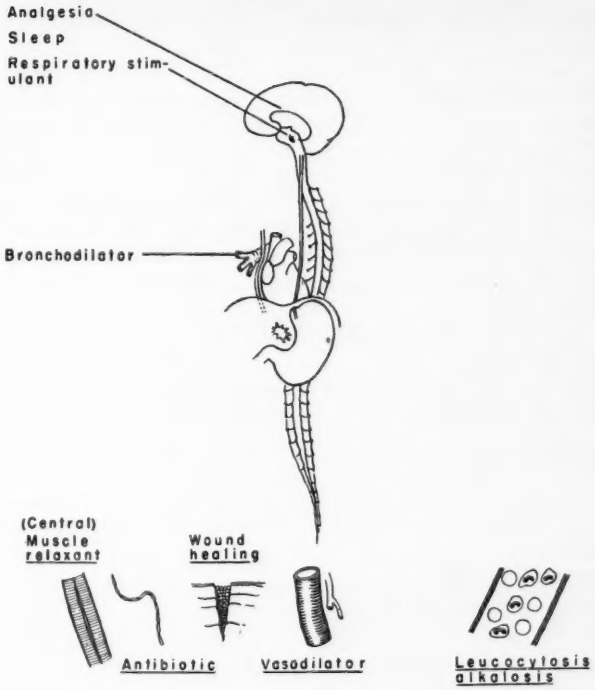


Fig. 1. Pharmacologic action of the phenothiazine derivatives: chlorpromazine, Phenergan, and Diparcol, as listed by Huguenard[2] and transposed into a diagram. (B) Functions that are enhanced.

Mélange No. 1

Phenergan*	50 mg.
Chlorpromazine (Thorazine**)	50 mg.
Demerol hydrochloride	100 mg.
Saline to make	12 ml.

After the last injection, which should be given 1¼ hours after the first one, refrigeration is started.

After the injection of Mélange No. 1, replace the 5 per cent glucose solution with Cocktail No. 1.

**Phenergan hydrochloride was provided by Dr. Daniel L. Shaw, Jr., of Wyeth Laboratories, 1401 Walnut St., Philadelphia, Pennsylvania.*

***Thorazine was provided by Mr. Edwin Boone, of Smith, Kline & French Laboratories, 1530 Spring Garden St., Philadelphia 1, Pennsylvania.*

Cocktail No. 1

Phenergan	150 mg.
Chlorpromazine	150 mg.
Demerol hydrochloride	150 mg.
Thiamine	200 mg.
Diparcol†	250 mg.
Glucose 5% to make	900 ml.

Cocktail No. 1 should be administered over a period of 18 hours (50 ml. per hour or about 12 drops per minute). Mark the specific height where the fluid level should be at two-hour intervals on the bottle with adhesive tape to insure a constant rate.

Second day:

Cocktail No. 2

Hydergine (Sandoz) (This is .9 mg. of equal parts of dihydroergotamine, dihydroergokryptine, and dihydroergocristine methane-sulfonates.)	3 ml.
Procaine	3-6 Gm.
Magnesium sulfate	6 Gm. (only if renal function is unimpaired)
Thiamine	200 mg.
Glucose 5% to make	900 mg.

Cocktail No. 2 also should run 18 hours.

Third day: (Warming up)

Cocktail No. 3

Thiamine	200 mg.
Ascorbic acid	1 Gm.
Ethyl alcohol	50 Gm.
Procaine	2-4 Gm.
Glucose 5%	1000 ml.
Normal saline to make	1800 ml.

Cocktail No. 3 should drip for 24 hours; this is at a rate of 75 cc. per hour.

Refrigeration is started after the last injection of Mélange No. 1. The patient is naked except for a "Bikini." Ice bags are applied on the axillae, on the groins and over the liver, or an electric fan is used to blow cool air over the patient to help refrigeration. Instead of ice bags, ice chips may have to be employed, or the patient may be put on a refrigerating mattress or wrapped in a refrigerating blanket through which ice water circulates. The room should be cool (windows open if it is cooler outside).

If shivering, restlessness, or other reactions occur, administer additional doses of 12.5 mg. Demerol hydrochloride alternately with 10 mg. of Nembutal into

†*Diparcol was supplied by Mr. R. Deville, of Rhodia Inc., 230 Park Ave., New York 17, New York.*

the tube of the intravenous infusion every ten minutes until the patient becomes quiet.

The body temperature is maintained between 32 and 34 degrees C. (between 90 and 93 degrees F.); overshooting is dangerous. Deep rectal temperatures are taken every half hour. (The rectum may be colder than the rest of the body if the patient is lying on an ice-water mattress.) Continue to apply ice when the temperature is down to 34 degrees C. (93 degrees F.) but remove it when the temperature is 33 degrees C. and the trend still is downward. Move the patient from side to side. If secreta accumulate in the trachea, frequent aspiration should be performed or tracheotomy may be necessary.

Blood pressure, pulse, and respirations should be followed and recorded at least every half hour.

Supportive therapy. Intramuscular administration of 100 mg. of growth hormone per day and Neodrol (androstanolone) or methylandrostenediol or testosterone 50 mg. per day are given for their supposed anabolic effect; heparin 50 mg. two times per day, is continued throughout the period of hibernation. If there are no contraindications, it is wise to increase the heparin dosage to 200 mg. per 24 hours intramuscularly during rewarming.

If **the hibernation must be continued over several days,** Cocktail No. 1 may be continued during the second day and, Cocktail No. 2 is given on the third day; these are alternated daily thereafter.

If **the patient is being allowed to warm up,** administer Cocktail No. 3.

Fluid and Electrolyte Requirements

During hibernation, fluid and electrolyte requirements are less than usual. If too much water is given there is great risk of overhydration. Fluid loss by drainage from gastric tubes or other drains must be replaced. Glucose is poorly utilized; the levels of blood sugar usually are high—around 200 mg. per cent. The administration of amino acid preparations is contraindicated if renal failure is present; otherwise it seems to be advantageous. Especially during induction of hibernation when the vasodilatation occurs—the blood volume may have to be replenished with dextran or blood. In patients with renal failure, it is best to use dextran 6 per cent in 5 per cent glucose rather than the commercial dextran that comes in normal saline.

Clinical Aspects of Artificial Hibernation

A patient who is anxious, fighting, restless, cyanotic, and miserable, becomes calm after induction of hibernation; he does not complain about pain; he appears to be sleeping but does respond. Complications are not masked. He will respond if you press on a broken leg or into a painful abdomen. There never is vomiting or hiccuping. Nails, ears, and lips are pink. In cases of ileus, the

TABLE
Experience with Artificial Hibernation in Nine Patients

Diagnosis and condition before hibernation. Age, sex	Indication for hibernation					Duration of hibernation	Additional therapy		
	High temperature	Low blood pressure	Ileus	Uncontrollable deterioration	Other factors		Artificial kidney	Trache-otomy	Other
1. *Traumatic pancreatitis*, crush syndrome, fractures, uremia. 34 yr. M	+	+	+	+	Restlessness	6 days	+	+	Craniotomy, cystoscopy
2. Aortic graft, *ischemic necrosis* of kidney, uremia. 57 yr. M	+			+	Convulsions	2½ days	+		Positive pressure respiration
3. Postpartum hemorrhage, hysterectomy, peritonitis, *hepatorenal syndrome*, focal renal cortical necrosis. 27 yr. F	+	+	+	+	Cyanosis	1½ days	+	+	
4. Cholecystectomy, *hepatorenal syndrome*, pancreatitis, biliary cirrhosis. 71 yr. M	+	+	+	+	Hypermotility, convulsions	2 days	+		
5. Peritonitis following appendectomy, *hepatorenal syndrome*, unknown. 44 yr. M	+	+	+	+		3 days			Laparotomy
6. Neurosurgical removal of meningioma; *cerebral edema*. 58 yr. F	+			+	Coma	4 days		+	
7. Exploration of common bile duct; *pancreatitis*. 58 yr. F	+	+	+	+	Restlessness	4 days			
8. *Arsenic poisoning*. 31 yr. F	+	+		+	Coma	2 days		+	
9. Exploration of common bile duct; *hepatorenal syndrome*, peritonitis, pancreatitis. 45 yr. F	+	+	+	+	Coma	3 days			
SUMMARY	9	7	6	9		1½ to 6 days	4	4	

TABLE (continued)

SUMMARY	9	7	6	9		1½ to 6 days	4	4	

TABLE (continued)
Experience with Artificial Hibernation in Nine Patients

Diagnosis and condition before hibernation. Age, sex	Apparent improvement after onset of hibernation	Life prolonged, days	Reason for failure	Difficulty in hibernation	Sensorium during warming up or at end	During hibernation	
						Diuresis per day	Uremia, mg. %
1. *Traumatic pancreatitis*, crush syndrome, fractures, uremia. 34 yr. M	++	5 days	Thrombosis and pulmonary embolism	Temperature too low	Good	50 cc.	220-550 mg. %
2. Aortic graft, *ischemic necrosis* of kidney, uremia. 57 yr. M	++	1½ days	Ischemic necrosis of kidney, pulmonary atelectasis, occlusion of femoral artery	Muscular rigidity, atelectasis	Improved	25 cc.	119-229 mg. %
3. Postpartum hemorrhage, hysterectomy, peritonitis, *hepatorenal syndrome*, focal renal cortical necrosis. 27 yr. F	+	?	Overwhelming infection, focal infarct, necrosis of kidneys	Low blood pressure		125 cc.	258 mg. %
4. Cholecystectomy, *hepatorenal syndrome*, pancreatitis, biliary cirrhosis. 71 yr. M	+	1	Bronchopneumonia	Respiratory failure	Uncertain	120 cc.	78-180 mg. %
5. Peritonitis following appendectomy, *hepatorenal syndrome*, unknown. 44 yr. M	Uncertain	?	Continued fall in blood pressure	Low blood pressure		1200-260 cc.	57+ mg. %
6. Neurosurgical removal of meningioma; *cerebral edema*. 58 yr. F	++	10 days	Recurrence of spiking temperature after 10 days	None	Improved	Maintained normal	
7. Exploration of common bile duct; *pancreatitis*. 58 yr. F	++	19 days	Cardiac arrest 3 weeks later, large retropancreatic abscess	None	Good	2000-3100 cc.	24 mg. %
8. *Arsenic poisoning*. 31 yr. F	+	1 day	Bronchopneumonia	Bleeding from tracheotomy		50 cc.	118+ mg. %
9. Exploration of common bile duct; *hepatorenal syndrome*, peritonitis. pancreatitis. 45 yr. F	+	1½ days	Atelectasis	Respiratory difficulty, nosebleed, fall in blood pressure		430-300 cc.	105-165 mg. %
SUMMARY	8	1 to 19 days					

distention becomes less. There are no shivering and goose pimples. The French authors stress the fact that they see no pulmonary complications. We have been less fortunate, but we started out with patients in whom these complications already were present or might be expected.

In a successful hibernation, a state is achieved that differs widely from coma, shock, or narcosis. It is characterized, according to Huguenard, by hypometabolism, hypothermia, hypotension (a systolic pressure that varies from 110 to 90), bradycardia, slow respiration, analgesia, half sleep (better called a state of disinterest), hyposecretion (of saliva, and bronchial, gastric, intestinal, bile, and pancreatic secretions), slowing of the circulation, prolongation of the clotting time, hyperleucocytosis, reduction of azotemia, alkalosis, hypovoltage of the electrocardiogram, and encephalographic waves of normal sleep.

Personal Experiences with Artificial Hibernation in Nine Patients

We have limited our attempts at hibernation to the treatment of patients who, with the currently available methods, but without hibernation, were considered by all concerned as hopelessly ill. The Table gives a summary of our experiences. Some of the patients had very complicated diseases, but the primary diagnoses are summarized as follows: Hepatorenal syndrome, 4; pancreatitis, 2; ischemic necrosis of the kidney, 1; postoperative cerebral edema, 1; and arsenic poisoning, 1.

The main indications for hibernation were the following conditions: high-spiking temperature, 9; uncontrollable deterioration, 9; uncontrollable fall in blood pressure (shock), 7; ileus with marked distention, 6; convulsions, extreme restlessness, and coma, each 2; cyanosis, 1.

In eight patients, apparent temporary improvement occurred after the onset of hibernation. Life was probably prolonged from 1 to 19 days in seven of the nine patients. The sensorium, as far as could be judged during temporary warming up or during the final warming-up period, improved in four of the nine patients.

The difficulties encountered during hibernation were as follows: temperature too low because of "overshooting," 1; muscular rigidity, 1; respiratory failure for unknown reason, 1; bleeding from nose and tracheotomy wounds into the trachea, causing atelectasis, 2; continued fall in blood pressure, 2. The diuresis decreased in five patients, and was maintained in two; in two oliguria had existed prior to hibernation. Azotemia increased in seven patients (up to 550 mg. urea per hundred ml. in one). The following two case reports are presented as examples.

Report of Cases

First case report (Fig. 2, Table). A 34-year-old man was in good health until he was in an automobile accident. He was admitted to a hospital, with a broken leg, a broken

pelvis, broken ribs, and bruises. On the sixth day he developed spiking temperatures. He was transferred to the Cleveland Clinic Hospital on the twelfth day. Extensive bruises and a large hematoma in the right side of the abdomen still were present. He was subicteric. The diaphragm on the right side was paralyzed. He was irrational and restless. His temperature was 40 degrees C. (103 degrees F.). He had uremic frost on his face; the blood urea was 290 mg. per hundred ml. An exact diagnosis could not be made, but it was thought that he might have a crush syndrome. A suspicion of pancreatitis was reinforced by a serum amylase higher than 1000 units.

At first he was treated conservatively. Intravenous infusions of 10 per cent invert sugar, sodium lactate and dextran were given, but the blood pressure fell to 80/60. Hibernation was started on the thirteenth day after the accident (Fig. 2). Dextran, 1 liter, had to be given to sustain the blood pressure around 95/60.

On the third day of hibernation, Cocktail No. 2 was started. On this day, the temperature dropped too low—to 23 degrees C. (73 degrees F.). P waves disappeared from the electrocardiogram; pulse rate was only 30; there was a markedly depressed ST with a negative T (Fig. 3). The temperature gradually came back to 29 degrees C. (85 degrees F.). The patient's color was pink; the electrocardiogram returned to normal (Fig. 3).

On the fifth day of hibernation he was treated with the rotating type of artificial kidney. The blood urea was reduced from 550 to 150 mg. per hundred ml. At times the

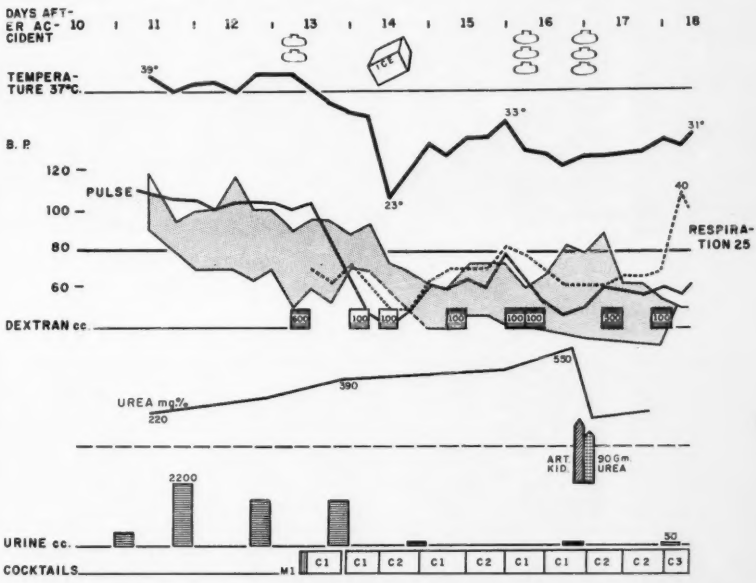
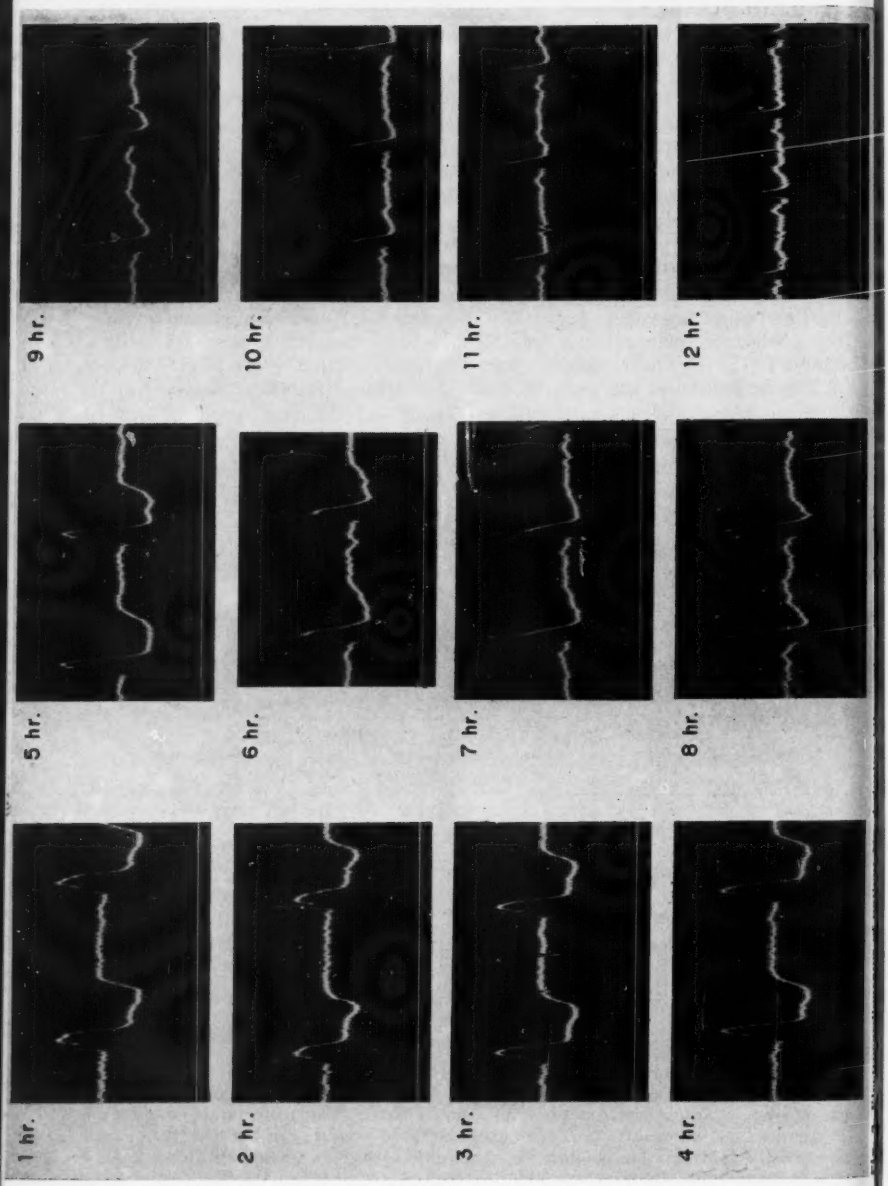


Fig. 2. (First case report, patient No. 1, Table) Hibernation was started where M1 indicates Mélange No. 1. Cocktails No. 1 and No. 2 were alternated. Ice bags and ice block in upper part of graph indicate when ice was applied. During overshooting, temperature went down to 23 degrees C. Dextran was required to keep the blood pressure up, but even then systolic pressure often was less than 80 mm. Hg. The urine volume decreased with the decrease in blood pressure.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patient was able to answer simple questions. On the sixth day, a rather sudden deterioration of his general condition occurred, with an increase in respiratory rate, cyanosis, and further fall in blood pressure. The patient died that day.

The postmortem examination revealed that multiple small pulmonary emboli were blocking the major part of the branches of the pulmonary arteries. These findings adequately explain the terminal deterioration.

Comment. We believe that this patient's life was prolonged for five days. The lethal complications might have been avoided by the administration of more heparin. We had given only 100 mg. per day because of the many hematomas and bruises present. Diuresis decreased, and the blood urea increased notwithstanding hibernation. Cystoscopy, trephination, treatment with the artificial kidney and a variety of minor procedures were performed without further anesthesia and without difficulty during the period of hibernation.

Second case report (Fig. 4, Table). A 58-year-old woman had recurrent attacks of pain in the right upper quadrant, one of which was associated with a rise in temperature, and she was reported to have been slightly icteric. The gallbladder had been removed 20 years before. The common duct was explored and a cholangiogram was made because the presence of a stone was suspected. No stone was found, and on the third day after

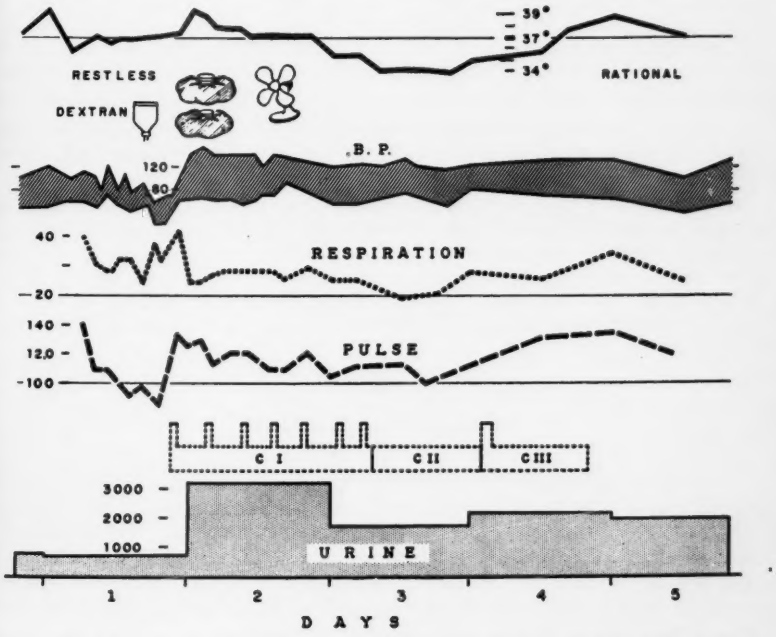

Fig. 4. (Second case report, patient No. 7, Table) Hibernation was started when the blood pressure was 60/40. CI, CII, and CIII indicate Cocktails Nos. 1, 2, and 3. The block-extensions above CI and CIII indicate use of additional Mélange No. 1. The spiking temperatures were controlled and blood pressure was maintained.

operation she developed a fulminating pancreatitis. Heart complications made their appearance, leading to intermittent partial block and at times auricular fibrillation. Her condition continued to deteriorate. She was extremely restless and had to be kept under heavy sedation. There were spiking temperatures up to 40 degrees C. (104 degrees F.), and recurrent falls in blood pressure, the last of which, on the twelfth day after the operation, failed to respond to the usual therapy—including the use of dextran. Her condition evidently was hopelessly deteriorating, and hibernation was started when the blood pressure was 60/40 and she no longer responded to any stimulus. No Demerol hydrochloride was added to the usual Mélange No. 1, as she was comatose already. During the onset of hibernation, the administration of dextran was continued. After a few hours, her blood pressure rose. The temperature increased and more Mélange No. 1 had to be given, this time with Demerol hydrochloride because the patient had awakened. Refrigeration was effected with the help of ice bags and an electric fan. The diagram in Figure 2 shows how Cocktail No. 1 was followed by Cocktails Nos. 2 and 3.

The patient's clinical condition improved from day to day. Cyanosis disappeared. Fluid and electrolyte therapy was continued in order to control losses by gastric and bile drainage. Urine volume increased to three and two liters per 24 hours. Abdominal distention regressed and when she was allowed to warm up on the fourth day, she proved to be clear of mind and cooperative. It seems that a vicious circle had been broken and that the patient then had a chance to recover.

Further convalescence progressed slowly but satisfactorily except for the recurrence of fever. Finally the fever disappeared, but she started to vomit; and one morning, 34 days after the operation and 19 days after the termination of the hibernation, she died suddenly while sitting in a chair.

As the electrocardiogram had continued to show a partial heart block, she probably died from cardiac arrest. At postmortem examination a large retropancreatic abscess was found.

Comment. The convinced hibernotherapist would see it thus: At a time that the body defenses produced spiking temperatures, restlessness, falling blood pressure and cyanosis, further deterioration was arrested by hibernation. The temperature was reduced and controlled; the blood pressure and oxygenation became adequate since cyanosis gave way to pink color. Distention regressed. It seemed that the infection was localized, and sensorium after awakening was clear. Unfortunately, though, the final outcome of the underlying disease was not altered.

Summary and Conclusion

Nine patients, all of whom were considered beyond recovery by more conservative methods, were treated with artificial hibernation. Uncontrollable deterioration, shock, spiking temperature, and restlessness were among the indications for hibernation. The technic of Laborit and Huguenard was followed as closely as possible. In seven patients a rapidly downhill clinical course seemed to be arrested, at least temporarily, and patients who seemed about to die lived 1 to 19 days during or after hibernation. Eight of the nine patients were more comfortable during hibernation. Such signs as spiking temperatures, ileus with distention, convulsions, extreme restlessness, and cyanosis gave way to controlled temperature, less distention, quiescence, and pink color. Two patients recovered

temporarily but finally died from the underlying disease. It is concluded that artificial hibernation deserves further trial in patients with potentially curable disease who presently would succumb to overwhelming aggression or during the struggle to overcome it.

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BLOOD VOLUME DETERMINATIONS IN THE OPERATIVE PERIOD

A Convenient, Simplified Procedure

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THE function of anesthesiology has been extended beyond the time of operation to involve preoperative evaluation and immediate postoperative management. The increasing magnitude of modern surgical procedures and the trend toward accepting for operation patients who are poor surgical risks place larger demands on the anesthesiologist's capacity to assess and to support the vital systems of the body. Blood volume is a major, determinable factor in this evaluation. Among the methods for its determination, those that use radioactive iodinated human serum albumin (I^{131})† are rapid and accurate and can be frequently repeated.

The normal average blood volume by this procedure is about 85 ml. per kilogram of body weight, of which blood cells make up some 40 ml. and plasma the remaining 45 ml. There is variation around this mean. Total blood volume is proportioned to the mass of metabolically active tissue. A lean, muscular person has a greater blood volume per unit of body weight than does an obese person. The aged tend to have smaller total blood volumes than the young. Determinations of hemoglobin content, red cell count, hematocrit ratio or plasma protein levels are made from a unit of the total volume. They give quantitative expressions of these components in relation to that volume, but they do not indicate what that volume may be. Hence, they do not substitute for direct determinations of total circulating volume (Table 1).

TABLE 1
Comparison of Findings on Three Blood Determinations in Various Conditions

Condition	Blood Volume	Hemoglobin	Hematocrit
Burns	Decreased	Normal to increased	Normal to increased
Shock	Decreased	Normal to increased	Normal to increased
Vomiting and diarrhea	Decreased	Normal to increased	Normal to increased
Acute bleeding	Decreased	Normal	Normal
Overtransfusion	Increased	Normal	Normal
Chronic bleeding	Decreased	Decreased	Decreased

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† *The radio-iodinated serum albumin (RISA) used in this investigation was supplied by the Abbott Laboratories on authorization from the Isotopes Division, U. S. Atomic Energy Commission.*

This report presents observations made with a simplified, isotopic technic that enables blood volume determinations to be made in anesthesiologic practice.

TECHNIC

Five milliliters of a reference solution containing about five microcuries of radioactive iodinated (I^{131}) human serum albumin is injected into an accessible vein. Care is exercised that no radioactive material is lost before injection and that the tip of the needle rests within the lumen of the vein. The syringe that contained the radioactive iodinated human serum albumin is rinsed twice with the patient's blood before the needle is withdrawn. Ten minutes is allowed for complete mixing of the isotope in the circulating blood of the patient. A longer period is required for patients who are hypotensive, cachectic, or seriously ill.

From another vein, 10 ml. of blood is withdrawn into a clean heparinized syringe. A portion of this blood is used to determine the hematocrit reading, and the remainder is sent to the isotope laboratory for determination of radioactivity. Five milliliters of the heparinized blood is accurately transferred into a test tube and placed in the well counter, where its radioactivity is measured on the scaler (Fig. 1). The total blood volume is determined using the formula:

$$\text{Total blood volume} = \frac{\text{Counts per minute of standard x ml. injected x dilution factor}}{\text{Counts per minute of patient's blood}}$$

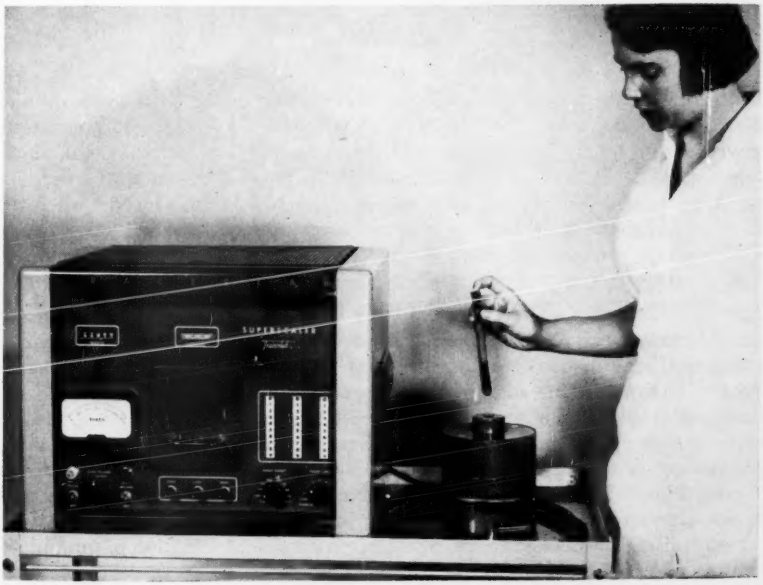

Fig. 1. Test tube being placed in the well counter where its radioactivity will be measured on the scaler.

The standard is prepared by dilution of the reference solution and its radioactivity estimated at the time of blood assay. The calculated total blood volume divided by the patient's usual body weight in kilograms gives the number of milliliters of blood per kilogram. Loss of weight during illness is disregarded. The total cell mass is calculated by multiplying the total blood volume by the hematocrit ratio as measured from the same sample of blood.

Validation of the Procedure

The accuracy of this method was tested in two ways. In one series of tests, 24 simultaneous measurements of blood volume were made using radioactive iodinated (I^{131}) human serum albumin and Evans blue. The mean difference in estimates between the two methods was 3.7 per cent. In the second series, blood volume determinations were made by the above procedure before and after blood donations. The amount of blood lost from the circulation was measured directly and also estimated from the differences in blood volume determinations. The mean difference between observed and estimated losses was 7.8 per cent. The greatest difference was 72 ml., the estimate being 572 ml. and the loss 500 ml.

APPLICATION

Preoperative. The method has particular value in the chronically ill[1] and the aged. These patients frequently are debilitated, have sustained great losses of weight and manifest contractions of blood volume and of the mass of circulating proteins. Patients with contracted blood volumes are subject to serious hypotension and circulatory collapse when anesthesia is induced,[2] when the plane of anesthesia is deepened, or when blood losses occur which do not seem of themselves remarkable. With the increasing amount of surgery performed on the older age group of patients, who are very often victims of chronic infection, malignancy, or prolonged drainage, this problem looms very large.

As noted above, routine laboratory procedures are of little help. An existing anemia may be masked by contraction of the plasma volume, so that hemoglobin content and hematocrit determination appear within normal limits. Similarly, contraction of plasma volume obscures a deficit in circulating protein mass, so that plasma protein determinations may also be within normal limits. The aim of preoperative care in such patients is to restore the specific deficit in total blood volume by appropriate means, so as to make them better able to withstand the stresses of anesthesia and surgery. This can be done with some precision by basing the treatment given on a determination of total blood volume and its fractions. Further, with advancing years there develops circulatory inadequacy such that overtransfusion is a serious risk, which a determination of blood volume would avoid.

Fig. 2. The syringes containing a calculated amount of isotope always are available in the recovery room refrigerator.

Operative. The need for an accurate estimate of blood loss during operation has been for years a challenge to surgeons and to anesthesiologists.[3] The technics used include estimating the hemoglobin content of washed sponges, and weighing the sponges used at the operating table. Both methods and their modifications have many sources of gross error. As indices of the desired postoperative replacement, they all depend on the assumption that the blood volume was normal preoperatively. All that they indicate is a crude estimate of the amount of blood lost during surgery, while they give no estimate of the amount of blood that may be needed to restore blood volume to normal. The intrinsic errors of these procedures preclude obtaining a good estimate of blood loss or blood requirements in specific operations; the variables include the skill of the surgeon, the duration of the operation and the complications that may be encountered. For these reasons, the only accurate method of estimating blood loss or determining blood requirement is to measure circulating

blood volume preoperatively and at intervals thereafter. The procedure described above, as was shown, can yield adequate estimates of comparatively small blood losses. It has the further advantage that the determinations can be repeated at frequent intervals.

Postoperative. Since it is possible to make repeated determinations, the method is useful also in the critical postoperative period. The only accurate basis on which to manage a blood replacement program is the periodic determinations of the total blood volume. Any rough estimates that are made during or after the surgical procedure can be accurately checked with a blood volume determination, the importance of which becomes even greater when repeated, comparative determinations can be made.

In many surgical procedures (e.g. transurethral prostatectomies, intracranial operations, and extensive dissections[4]) there is an appreciable blood loss postoperatively that may be almost as great as the blood loss during operation. Without help from the laboratory, the replacement of this loss is left to the judgment of the clinician and again overtransfusion remains just as great a hazard as undertransfusion.

DISCUSSION

The safe administration of anesthesia extends beyond provision of an adequate oxygen and carbon dioxide transporting mechanism. All too frequently deficiencies in total circulating volume are masked in spite of the laboratory procedures that evaluate the hemoglobin concentration, the cell mass, and the red cell count (Table 2). The preoperative use of blood volume determinations permits accurate evaluation of the circulatory volume and the necessary preoperative treatment of any deficiencies. In the chronically ill and aged patients, contracted blood volumes many times are not recognized (Table 2, Case 2) unless blood volume determinations are made. If such states were properly diagnosed and then the patients were transfused with whole blood, the circulatory instability during the operative procedure would be greatly reduced.[5]

The two more common methods of determining circulating[6] blood volume are the Evans blue method (T-1824) and that using radioactive iodinated serum albumin. There are other methods involving the use of other isotopes, but each has practically insurmountable obstacles to its use.[7] In this study, each patient was tested both by the Evans blue and by the radioactive iodinated serum albumin method simultaneously. There was no clinically significant difference in the results. In contrast with the dye method, the isotope method using I^{131} has several advantages: it can be repeated; it does not interfere with the use of other colorimetric laboratory procedures; the preparation for administration of the isotope is minimal. The syringes containing a calculated amount of isotope are always available in the recovery room refrigerator (Fig. 2). After injecting the contents of one syringe, allowing 10 to 15 minutes for mixing in the blood stream, the blood sample for counting is withdrawn and

sent to the isotope laboratory. As many determinations as are necessary can be made for the individual patient. The calculated blood volume and the plasma volume, as previously described, disclose deficiencies of specific blood components which can be treated by specific replacement therapy. Such a program is well appreciated in the case of polycythemia.[8]

TABLE 2

Hemoglobin and Hematocrit Determinations Compared with Blood Volume in Various Conditions and Stages of Surgical Procedure

Case No.	Status		Age (yr.)	Hemoglobin Gm./100 ml.	Hematocrit %	Blood Volume ml./Kg.
1	Preoperative	Bleeding gastric ulcer	41	13.5	47	47
2	Preoperative	Carcinoma of colon	82	13.2	44	58
3	Preoperative	Embolus, femoral artery	—	14.2	54	80.5
	Postoperative	Arterial embolectomy	—	13.5	49	74
4	Preoperative	Diabetes and gangrenous leg	—	15	48	47
5	Postoperative	Retroperitoneal leiomyosarcoma	—	9.5	27	80.5

The use of blood volume determinations during surgical procedures does not relieve the anesthesiologist and surgeon of the responsibility of blood replacement. In many instances, the operative team can estimate blood loss with considerable accuracy. However, in the longer operative procedures and especially in those in which the blood loss is considerable, clinical estimation of the hemorrhage many times is inaccurate. In those instances, the determination of the circulating blood volume would replace supposition with fact.

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THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces the Third Annual Postgraduate Continuation Course in Pediatrics for September 28 and 29, 1955

Current Therapy in Pediatric Practice

Wednesday, September 28, 1955

8:00- 8:55 a.m.	Registration	
	Morning Session	VIOLA STARTZMAN, M.D., PRESIDING
8:55- 9:00 a.m.	Welcome	F. A. LEFEVRE, M.D.
9:00- 9:20 a.m.	Obstetrical Complications and Neonatal Death	H. P. TAYLOR, M.D. *
9:20-10:00 a.m.	Clinical Pathologic Conference: Vomiting and Jaundice in the Newborn	
	Discussant	R. G. HODGES, M.D. *
	Pathologist	B. J. LANDING, M.D. *
10:00-10:20 a.m.	Intermission	
10:20-10:35 a.m.	Treatment of Infantile Eczema	E. W. NETHERTON, M.D.
10:35-11:05 a.m.	Abnormal Breathing	C. J. WIGGERS, M.D.
11:05-11:50 a.m.	Pulmonary Disease of the Newborn	B. J. LANDING, M.D. *
11:50-12:10 p.m.	Questions and Answers	
12:10- 1:45 p.m.	Luncheon—Courtesy Bunts Institute	
	Afternoon Session	R. D. MERCER, M.D., PRESIDING
2:00- 2:30 p.m.	Erythroblastosis	VIOLA STARTZMAN, M.D.
2:30- 3:00 p.m.	Common Sense and Cancer Surgery	GEORGE CRILE, JR., M.D.
3:00- 3:20 p.m.	Intermission	
3:20- 3:35 p.m.	Hypothermia in Pediatric Anesthesia	C. E. WASMUTH, M.D.
3:35- 4:20 p.m.	Case Presentation and Seminar: Recurrent Respiratory Infections	R. N. WESTCOTT, M.D. VIOLA STARTZMAN, M.D. R. R. EVANS, M.D. C. W. HOCH, M.D.
4:20- 4:40 p.m.	Questions and Answers	

Thursday, September 29, 1955

	Morning Session	R. D. MERCER, M.D., PRESIDING
9:00- 9:15 a.m.	The Infantile Patent Ductus	D. B. EFFLER, M.D.
9:15- 9:30 a.m.	The Treatment of Uremia	W. J. KOLFF, M.D.

9:30-10:10 a.m.	Clinical Pathologic Conference: Overwhelming Pulmonary Disease, Hepatosplenomegaly and Death Discussant . . . . . W. H. Borges, M.D.* Pathologist . . . . . J. B. Hazard, M.D.
10:10-10:30 a.m.	Intermission
10:30-10:45 a.m.	The Care of Deciduous Teeth . . . . . C. A. Resch, D.D.S.
10:45-11:00 a.m.	Congenital Anomalies of the External Genitalia . . . . . Robin Anderson, M.D.
11:00-11:15 a.m.	The Treatment of Mild Respiratory Allergy . . R. R. Evans, M.D.
11:15-12:00 noon	Case Presentation and Seminar: Abnormalities of the Lower Spine and Spinal Cord . . . . . W. J. Gardner, M.D. A. W. Humphries, M.D. D. D. Matson, M.D.* R. D. Mercer, M.D. E. F. Poutasse, M.D.
12:00 noon-1:45 p.m.	Luncheon—Courtesy Bunts Institute
	Afternoon Session . . . . . Viola Startzman, M.D., Presiding
2:00- 2:15 p.m.	The Treatment of Severe Respiratory Allergy . . . . . C. R. K. Johnston, M.D.
2:15- 3:00 p.m.	The Treatment of Head Injury . . . . . D. D. Matson, M.D.*
3:00- 3:15 p.m.	Pneumoencephalography . . . . . A. S. Tucker, M.D.
3:15- 3:35 p.m.	Intermission
3:35- 3:50 p.m.	Colic and Feeding Problems . . . . . C. Q. McClelland, M.D.*
3:50- 4:20 p.m.	The Year in Pediatrics . . . . . R. D. Mercer, M.D.
4:20- 4:30 p.m.	Questions and Answers

Guest Speakers

H. P. TAYLOR, M.D.: Chief of Obstetrics, Booth Memorial Hospital; Associate in Obstetrics and Gynecology, St. Luke's Hospital; Cleveland, Ohio.

R. G. HODGES, M.D.: Pediatrician-in-Chief, St. Luke's Hospital; Associate Clinical Professor of Preventive Medicine and Assistant Clinical Professor of Pediatrics, Western Reserve University; Cleveland, Ohio.

B. J. LANDING, M.D.: Directing Pathologist, Children's Hospital and Children's Hospital Research Foundation; Assistant Professor of Pathology and Pediatrics, University of Cincinnati; Cincinnati, Ohio.

W. H. BORGES, M.D.: Assistant Professor of Pediatrics, Western Reserve University; Cleveland, Ohio.

D. D. MATSON, M.D.: Associate Clinical Professor of Surgery, Harvard Medical School; Neurosurgeon, Children's Medical Center; Senior Associate in Neurosurgery, Peter Bent Brigham Hospital; Boston, Massachusetts.

C. Q. McCLELLAND, M.D.: Instructor in Pediatrics, Western Reserve University; Cleveland, Ohio.

* *Guest speaker.*

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ANNOUNCEMENTS

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announces a postgraduate continuation course

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October 26 and 27, 1955

Sponsored by

The Department of Gastroenterology

The course will include discussions of the surgical as well as the medical aspects of diseases of the gastrointestinal tract, demonstrations of the newer roentgenographic technics used in the diagnosis of hiatus hernia, jejunal ulcer, diverticulum, and papilla of the colon, with special attention to intravenous cholangiography (Cholografin), and a practical demonstration of special laboratory procedures.

A final program will appear in the October issue of this journal. For details of this program prior to October, please contact the Secretary of The Frank E. Bunts Educational Institute, 2020 East 93 Street, Cleveland 6, Ohio.

CHANGES IN THE FUNDUS OCULI IN RELATION TO HYPERTENSION

GEORGE LOCKHART, III, M.D.
Department of Ophthalmology

AN understanding of the relationship of changes in the fundus oculi to grades of hypertension is important alike to the internist and the ophthalmologist. Various approaches to the study of the relationship have been suggested. These have been based on arbitrary classifications of ophthalmoscopic changes and hypertensive states, the early reports of which were those of Keith, Wagener and Barker[1] in 1939, and of Wagener, Clay and Gipner[2] in 1946. Wilson,[3] in 1952, compared the two studies and suggested that a working combination of both classifications could be used. I have found the combination to be a practical basis for evaluating the over-all vascular status of the patient. Recently Minsky[4] introduced a scheme of correlating ocular changes with diastolic blood pressure. To each type of retinal change he assigned a specific numerical value that he used in a mathematical formula to calculate the expected diastolic pressure. It is too soon as yet to assess the value of this procedure.

OCULAR MANIFESTATIONS OF HYPERTENSION

The ophthalmoscopic changes associated with hypertension may be classified into two groups: (1) *Angiopathy*, which includes generalized and focal vascular sclerosis and narrowing of arterioles; and (2) *Retinopathy*, which includes hemorrhages, exudates, neovascularization, papilledema, and macular stars.

Angiopathy

Recognition and Grading of Sclerosis

There still is much confusion in regard to recognition and grading of sclerosis in the fundus oculi. The chief problem is to differentiate between atherosclerosis and arteriolar sclerosis. Only the central retinal artery and the larger branches near the disc are true arteries. At about the first or second bifurcation, the retinal arterial tree becomes arteriolar in nature as the internal elastic lamina disappears, and gaps appear in the continuity of the fibers of the muscularis. These changes take place at a vascular diameter of about 75 microns.

Scheie[5] has graded separately the hypertensive changes and those of arteriolar sclerosis, and has stressed the different types of arteriosclerosis. He particularly emphasized the differentiation of ophthalmoscopic changes in atherosclerosis and in arteriolar sclerosis. He included both general attenuation and focal constrictions of arterioles under hypertensive changes; however, I believe

that these signs should be considered separately since each has a different significance.

Atherosclerosis. Atherosclerosis usually is associated with the aging process, but it may begin early in life. It is a disease of the intima and is patchy in distribution. The primary lesions or atheromata are small, yellow, elevated areas of intimal thickening. The internal elastic lamellae become fragmented; proliferation of connective tissue takes place and deposition of cells and fibers containing cholesterol crystals and lipid droplets occurs. Hyalin degeneration and calcification subsequently may develop. There is a marked disparity between the extent of atherosclerosis and the degree of function of the organ supplied by the affected vessels: function is not disturbed until relatively late in the course of the disease; blood pressure may be normal even in advanced atherosclerosis.

On ophthalmoscopic examination, atherosclerosis in rare instances may be seen as an atheromatous plaque in a retinal arteriole. The plaque appears as a shining spot of yellowish color on an arteriole, usually at a bifurcation; the shining appearance is caused by the deposit of cholesterol crystals. However, the ocular involvement often is in the central retinal artery within the substance of the optic nerve and usually can be diagnosed only by inference. Often the first visible sign of atherosclerosis is occlusion of the central artery or vein, or of one of their branches. In that location a venous obstruction may be caused by atherosclerosis, since the artery and vein are immediately adjacent with their walls touching and they are surrounded by common bands of connective tissue. The vein may be compressed or may be invaded by the atheromatous plaque and thereby become obliterated. In the central retinal artery, there may be no ophthalmoscopic evidence of atherosclerosis even though obstruction is imminent. Often the earliest clue is the presence of choroidal sclerosis that is first seen in the inferior nasal quadrants and, in the early stages, appears similar to the usual tessellation seen in the fundi of blond or brunette persons. First the choroidal vessels stand out as reddish streaks, then yellow, and finally in advanced stages as white streaks. Choroidal sclerosis is a sign of atherosclerosis and not of hypertension, although it frequently is seen in hypertension.

Arteriolar sclerosis. Arteriolar sclerosis is caused by hypertension and represents damage to the walls of the vessels from the stress and strain of elevated blood pressure. Pathologically, the vascular walls show diffuse involvement with deposits of hyalin and lipid just outside the endothelium. As the disease progresses, the muscularis and finally the entire thickness of the wall are involved. The changes seen in the retinal arterioles reflect the condition of arterioles throughout the body and have been well correlated with changes in the renal arterioles.[6,7]

Arteriolar sclerosis may be chronic or acute in formation. Chronic arteriolar sclerosis is a generalized sclerosis and may develop slowly over a period of years. Generalized arteriolar sclerosis is characterized by the absence of focal lesions, the vascular walls being smooth and without indentations. The degree of sclerosis is determined by the extent of arteriovenous crossing defects. Acute arteriolar sclerosis may develop rapidly when there is severe, active hypertension. This follows the hypertensive picture: first there is generalized narrowing

of arterioles, then focal angiospasm, then focal sclerosis. The degree of focal sclerosis is determined by the depth of focal sclerotic constrictions. The prognosis is worse in the acute type of arteriolar sclerosis than in the chronic type.

A secondary form of arteriolar sclerosis is caused by edema and fibrosis resulting from localized disease in the retina. This secondary form occurs most commonly near areas of chorioretinitis. The differentiation between generalized arteriolar sclerosis of hypertension and secondary arteriolar sclerosis is best made on the basis of the distribution of sclerosis. Hypertensive arteriolar sclerosis involves peripheral vessels first and then progresses centrally toward the larger vessels. Secondary arteriolar sclerosis may begin anywhere in the retina, depending upon the location of the primary inflammation. Sheathing of the arterioles is a form of secondary sclerosis caused by edema or retinopathy that often is seen in hypertension.

Grading of Arteriolar Sclerosis

The grading of the severity of arteriolar sclerosis is based upon two factors: the arteriolar light reflex, and the arteriovenous crossing defects. The second of these is the most important. Many different signs have been described as indications of arteriolar sclerosis, but all result from thickening of the walls of the arterioles and associated changes in the veins at the arteriovenous crossings. The arterioles and the veins have a common adventitial coat at their crossings. The earliest sign is compression of the veins, and this may vary in severity from the slightest indentation to nearly complete interruption of the vein at the point of crossing. Other signs include (1) deviation of the vein from its normal course at the point of crossing, (2) humping of the vein where it crosses an artery, (3) tapering caused by extension of the sclerotic process into the adventitia of the vein, and (4) banking caused by some obstruction to the venous return at the point of crossing.

A satisfactory grading of the *severity of arteriolar sclerosis* is as follows (Fig. 1):

Grade I Widening and increased brightness of the arteriolar-reflex stripe, and obscuration of the vein at point of crossing, with slight indentation of veins.

Grade II Copper-wire reflex, indentation of veins and clear spaces on side of crossing arterioles.

Grade III Silver-wire reflex, marked crossing defects, with tapering, banking, humping, and right-angled deflections.

Grade IV White fibrous cords with no blood column.

The terms *copper-wire* and *silver-wire* reflexes are somewhat misleading, since arteriolar light reflexes exactly described by these terms seldom are seen. In children and young adults with clear media, the normal arteriolar light reflex may be very brilliant. In Negroes the normal light reflex also often is unusually bright and may lead to errors in interpretation.

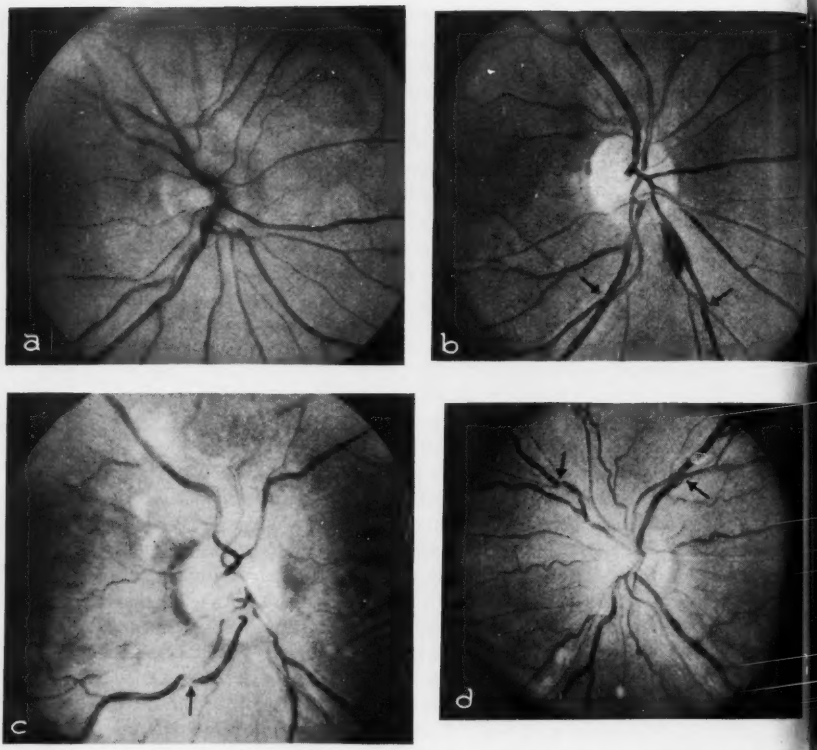

Fig. 1. Arteriolar sclerosis: (a) Normal. (b) Grade I. (c) Grade III. (d) Grade II.

Grading of Arteriolar Constriction

The second factor to be graded is constriction of the arterioles. Two types are found: (1) generalized attenuation that is due to tonic contraction of the vascular walls, and (2) focal constriction that is attributed to localized spasm. The earliest ophthalmoscopic change in hypertension is a generalized attenuation of arterioles. This is best seen in toxemia of pregnancy or in acute hypertension of rapid onset. The extent of narrowing is fairly proportional to the degree of elevation of blood pressure. In early cases it is seen first in the nasal quadrants beyond the second bifurcations. As mentioned earlier, I prefer to grade generalized and focal constrictions separately. Generalized narrowing almost always is present in organic hypertension; on the other hand, focal spasm indicates actively progressive disease and a more severe hypertension with a correspondingly poorer prognosis.

A suitable grading of the *severity of arteriolar constriction* is as follows:

Generalized (Fig. 2)

Grade I Slight narrowing—most noticeable in nasal periphery.

Grade II More marked narrowing with A/V ratio of about ⅓.

Grade III Very marked narrowing, A/V ratio of about ¼.

Grade IV Arterioles threadlike or invisible.

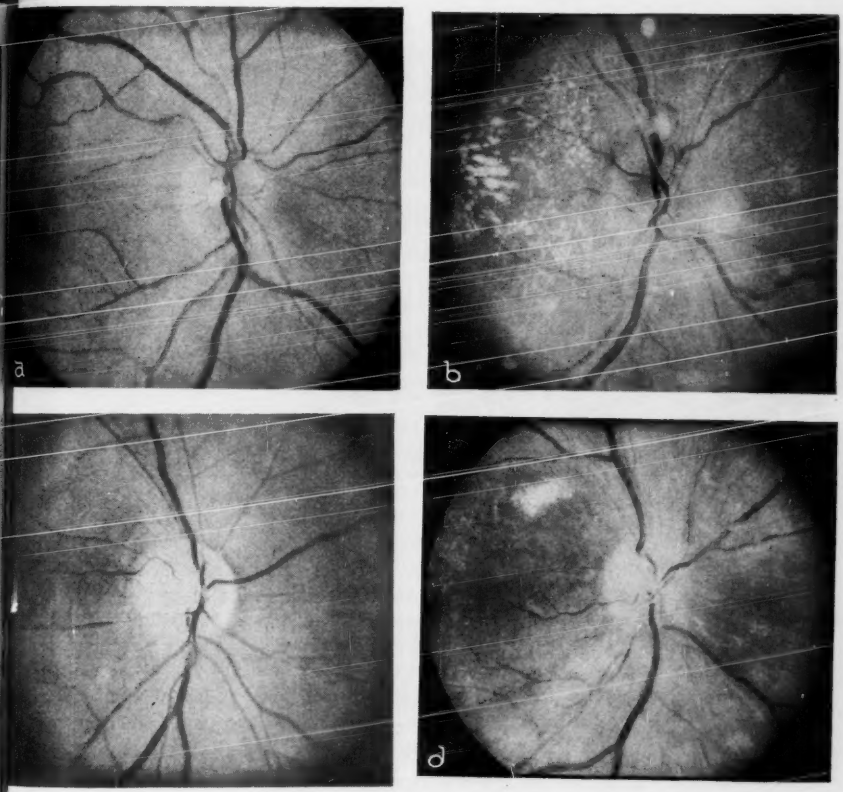

Fig. 2. Generalized arteriolar attenuation: (a) Grade I. (b) Grade II. (c) Grade III. (d) Grade IV.

Focal (Fig. 3)

Grade I Few areas of slight localized narrowing.

Grade II Many areas of narrowing to ½ size of proximal segment.

Grade III Local narrowing to threadlike size.

Grade IV Arterioles invisible at points of constriction.

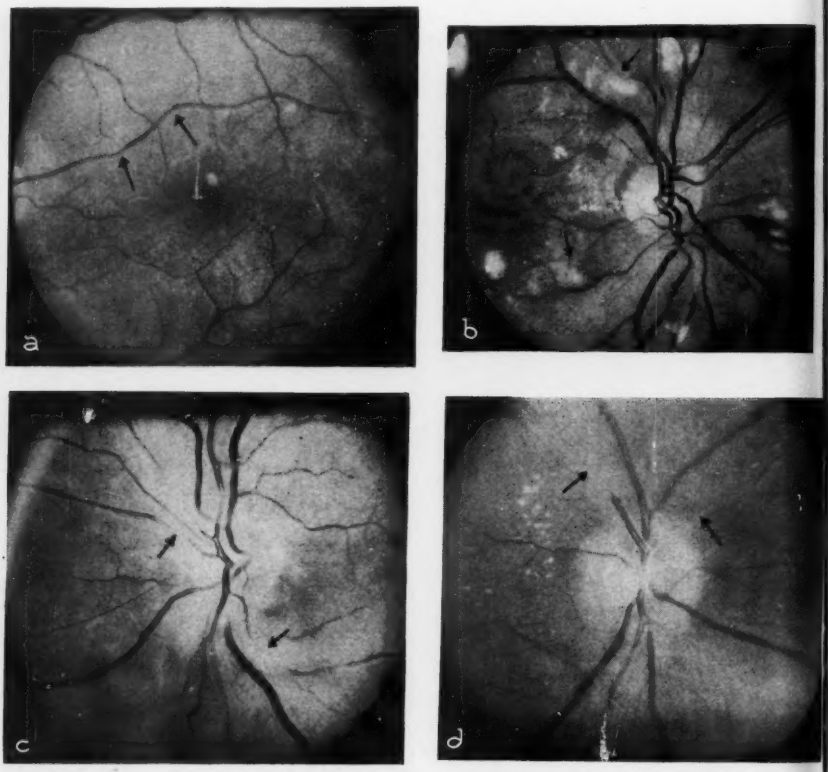

Fig. 3. Focal arteriolar constriction: (a) Grade I. (b) Grade II. (c) Grade III. (d) Grade IV.

Retinopathy

The next factor to be graded is retinopathy. Hemorrhages, exudates, and edema also are manifestations of the hypertensive picture.

Grading of Hemorrhages. Hemorrhages are graded 1 to 4 depending upon the number of ocular quadrants involved. The area of each eye, for observational

purposes, is arbitrarily divided into four quadrants; normally there are eight quadrants to observe. Hemorrhage in one or two quadrants is grade 1; in three or four quadrants is grade 2; in five or six quadrants is grade 3; in seven or eight quadrants is grade 4. This grading system is more accurate than counting the number of hemorrhages or estimating the total number, since a number of hemorrhages in one quadrant may be due to one spastic or damaged vessel; whereas, only a few in each of four or five quadrants certainly indicates a more widespread pathologic condition. Localized retinopathy from an occlusion of a venous branch is not graded as part of the hypertensive picture, but is listed as a complication.

Exudates. The term *exudate* is a misnomer since the appearance of whitish spots is not associated with actual inflammation, but the term is retained because of common usage and understanding. Exudates may be of two types: (1) Cotton-wool patches are seen as soft, white areas with feathery borders and are caused by localized edema, deposits of fibrin, or cytoid-body formation due to pre-capillary occlusion or spasm. Cotton-wool patches are graded, as are hemorrhages, according to the number of quadrants involved. They characteristically appear during acute phases of hypertension and may change appearance within three or four days. They usually take several weeks to disappear and may last for months. (2) Hard exudates or edema residues are deposits of hyalin or lipid in the deeper layers of the retina, and usually appear later than the cotton-wool patches; i.e., after the acute phase of hypertension has been present for a longer period of time, or when it is subsiding. These deposits frequently are seen in the macular region where they assume the appearance of the radiating-star figure because of the histologic configuration of Henle's layer. They are not graded numerically since their presence is not necessarily related to the course of the disease under treatment. They may last many months or even remain permanently.

Papilledema indicates the most severe hypertensive states and may be confined to the disc itself, or spread out in the surrounding retina. If edema is widespread over the retina, it may give rise to serous retinal detachment that subsides with control of the hypertensive state and absorption of edema.

Other Factors. Several other factors are noted and taken into consideration although they are not graded. Neovascularization indicates that occlusion or partial occlusion of vessels has previously occurred during active episodes of hypertension. Neovascularization of the disc often is seen after papilledema has subsided. Sheathing of vessels is not taken into account when grading generalized sclerosis; instead, it is listed separately as indicating previous angiospasm and edema. As mentioned before, vascular sheathing is a form of secondary arteriolar sclerosis. Sheathing of the larger vessels on the disc may be a normal variation. Elschnig spots appear as spots of pigment in the choroid with reddish or yellowish halos, and supposedly are caused by patchy distribution of the sclerotic process in the choriocapillaris; the overlying pigment disappears in certain areas to form the red or yellow halos, and accumulates in other areas to form the pigment spots. Siegrist streaks are chains of pigmented spots arranged

like a string of beads along a white and sclerotic choroidal vessel over which the pigment epithelium has been affected. The significance of Elschnig spots and Siegrist streaks is not well understood, but when they are widespread the prognosis must be more guarded.

SEVERITY OF HYPERTENSION IN RELATION TO OCULAR MANIFESTATIONS

Hypertensive changes have been variously grouped; the most widely used grouping as well as the simplest is the Keith-Wagener classification.[1] This classification is based on the over-all clinical status of the patient, and includes evaluation of cardiac and renal function and cerebrovascular and ophthalmoscopic changes.

Keith-Wagener Classification

Group I Minimal or no changes in all four systems. Fundi may show grade I arteriolar attenuation and sclerosis. The patient has no symptoms.

Group II Moderate-to-marked angiopathy with attenuation and sclerosis, but no retinopathy. However, there may occasionally be venous occlusions due to atherosclerosis. Other systems are affected, but function is adequate.

Group III Angiopathy and retinopathy present with hemorrhages and exudates. Patient almost always has symptoms. Other systems definitely affected.

Group IV Ocular signs, as in *group* III, with papilledema. Patients have serious impairment of cardiac or renal functions. Encephalopathy is frequent. Symptoms are severe.

I believe the best single classification is that proposed by Wagener, Clay and Gipner,[2] which was accepted by the American Ophthalmological Society. Hypertension is categorized into five types[2]: (A) *Neurogenic*, (B) *Chronic nonprogressive*, (C) *Chronic progressive*, (D) *Acute angiospastic*, (E) *Terminal malignant*.

Wagener-Clay-Gipner Classification

A. *Neurogenic hypertension*—Nothing in retina, except slight generalized attenuation

B. *Chronic nonprogressive hypertension*
   1. Grades I or II generalized attenuation of arterioles
   2. Grades I or II generalized arteriolar sclerosis (seen after disease has been present for several years)

C. *Chronic progressive hypertension*
   1. Generalized arteriolar sclerosis, always
   2. Generalized attenuation of arterioles
   3. Focal constrictions in arterioles
   4. Focal arteriolar sclerosis, occasionally
   5. Cotton-wool patches and hemorrhages, occasionally

D. *Acute angiospastic hypertension*

1. No arteriolar sclerosis
2. Generalized narrowing of arterioles
3. Focal constrictions in arterioles
4. Edema of retina, cotton-wool patches, hemorrhages
5. Edema of disc, often

E. *Terminal, malignant hypertension*

1. Generalized arteriolar sclerosis, always
2. Papilledema, always
3. Generalized attenuation of arterioles
4. Focal constrictions in arterioles
5. Edema, hemorrhages, cotton-wool patches, edema residues, macular stars

From the foregoing classification it can be seen that the presence of papilledema is not pathognomonic of malignant hypertension unless it is accompanied by arteriolar sclerosis. If ophthalmoscopic changes with papilledema are present but arteriolar sclerosis specifically is absent, the condition is classified as *acute angiospastic hypertension;* the course may progress to complete resolution, to chronic hypertension, or to malignant hypertension and death.

I have found a combination of these two classifications, the Wagener-Clay-Gipner and the Keith-Wagener, to be the most useful for evaluating changes in the fundus in relation to hypertension. After describing and grading the ophthalmoscopic changes, the impression is given as *chronic nonprogressive hypertension, group I,* or *chronic progressive hypertension, group II,* or any applicable combination as the particular case warrants. A supplementary notation may then be added indicating corollary impressions, such as evidence of previous papilledema or angiospastic episodes.

The grade of arteriolar sclerosis indicates the probable duration of the hypertension—a fact that often is difficult to deduce from the history. When the arteriolar sclerosis is minimal (grade I) or is absent, the hypertension most likely is of recent origin or is of neurogenic type. When arteriolar sclerosis is marked (grades III or IV) the hypertension is likely to be of long standing, although the more severe the hypertension the more rapidly sclerosis develops. The severity of hypertension usually can be assessed more readily by the internist. However, marked narrowing and focal constrictions of arterioles sometimes indicate severe hypertension when the blood pressure is normal or only slightly elevated; this condition may occur in a patient whose blood pressure has dropped as a result of coronary thrombosis or cardiac failure. Focal constrictions indicate more active hypertension than does generalized arteriolar constriction. Neovascularization and sheathing indicate previous angiospastic episodes and give a clearer picture of the history and prognosis of the disease.

Hemorrhages, exudates, and edema indicate active hypertension with breakdown of vessels. These changes are graded chiefly as a means of ascertaining the response of the patient to treatment; their disappearance indicates a favorable response. Early attenuation or mild focal constriction likewise may be lessened by treatment, but sclerosis is permanent and does not respond (Fig. 4).

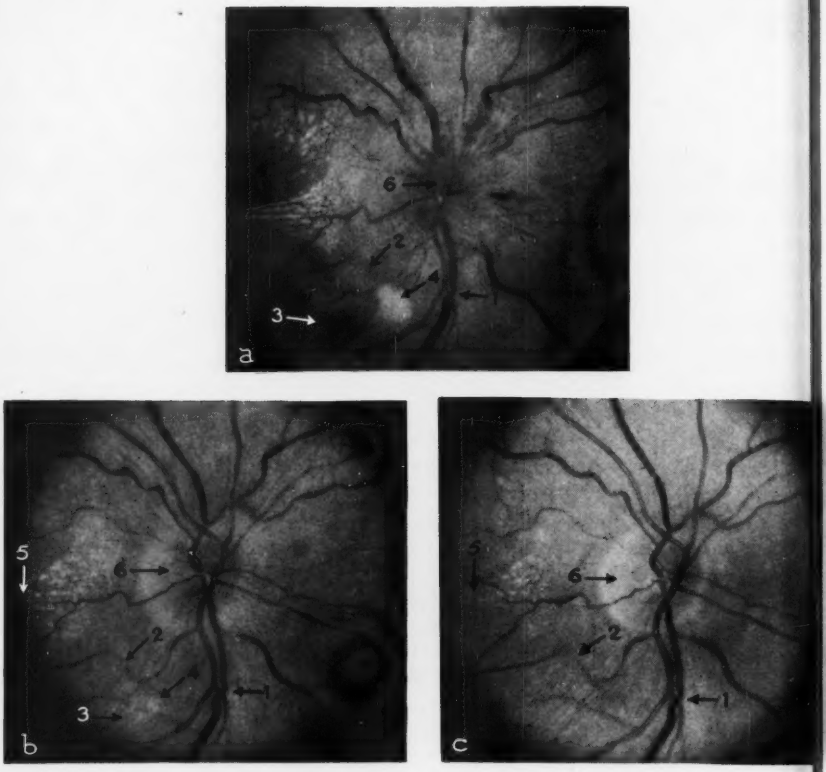

Fig. 4. Malignant syndrome with favorable response to treatment: (a) July 16. (b) Aug. 24. (c) Oct. 14. (1) Arteriolar sclerosis remains unchanged. (2) Arteriolar spasm lessens. (3) Hemorrhage is absorbed. (4) Cotton-wool patch disappears. (5) Macular star decreases. (6) Papilledema subsides.

Summary

Ophthalmoscopic changes in hypertension have been described, and the systems of grading and classification have been discussed, in an effort to clarify their value in determining the clinical status of hypertensive patients. Ophthalmoscopic examination in a hypertensive patient yields information concerning the appearance of the fundi and the status of arteriolar sclerosis, generalized attenuation, focal constrictions, hemorrhages, exudates, edema, neovascularization, sheathing, and choroidal changes. After examination and description of the fundi, the appropriate changes are graded and the over-all picture is then classified in terms of the Wagener-Clay-Gipner and the Keith-Wagener systems;

for example, *chronic progressive hypertension, group III.* When this method is followed, the ophthalmologist can be of great help to the internist in the evaluation of the hypertensive patient.

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CHRONIC SUBDURAL HEMATOMA

*Historical Review and Analysis of 60 Cases**

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CHRONIC SUBDURAL HEMATOMA has been well described in the literature. Initial descriptions were published several centuries before 1857, when Virchow's paper,[1] now considered a classic, first presented a clear account of the histopathologic nature of the lesion and suggested an explanation of its origin. Putnam and Cushing[2] in 1925 discussed the neurosurgical aspects, and Gardner[3] in 1932 offered a plausible explanation of the delayed development of symptoms. The purpose of this report is to present a brief historical review together with an analysis of the cases of 60 patients seen and treated at the University Hospital in Copenhagen.

Etiologic Aspects

Trauma is believed generally to be the most important cause of a subdural hematoma. However, although demonstrable in nearly all acute cases,[4,5] in a high percentage of chronic cases there is no traceable history of injury. Virchow[1] recognized that the lesion sometimes was traumatic, but he believed that chronic subdural hematoma (which he called "pachymeningitis chronica hemorrhagica") was most often caused by chronic inflammation of the dura with extravasation of blood into the subdural space and formation of a film of fibrin over the inner surface of the dura. Sperling[6] in 1872 reported that whole blood injected into the subdural space resulted in formation of membranes that in many respects were similar to those of chronic subdural hematoma. Huegenin[7] in 1877 reported that he frequently found fatty degeneration, sometimes thrombosis, and occasionally rupture of the veins of the pia. Barrett[8] in 1902 stated that the pathologic findings did not appear to be inflammatory and that the formation of a film of fibrin over the inner surface of the dura (an important point in Virchow's theory) did not prove the presence of inflammation.

Kasemeyer[9] in 1911, and Henschen[10] in 1912 showed that delayed symptoms frequently occurred in traumatic cases of subdural hematoma. Trotter[11] in 1914 and Putnam and Cushing[2] in 1925, in their respective series, found that a definite history of trauma usually could be obtained. Putnam and Cushing stated that they had found no case of nontraumatic hematoma of the dura without some precedent disease. However, later authors [5,12] do not agree that there always is a precedent disease in cases of "nontraumatic" hematoma.

**Study made while the author was in the Department of Neurosurgery, University Hospital (Rigshospitalet), Copenhagen, Denmark; Chief, Professor E. Busch, M.D.*

Solely on the basis of the literature mentioned, it is difficult to understand why the viewpoint has changed so completely from that expressed by Virchow. Some of the reasons may be: (1) later authors [4,12] have substantiated the findings of Putnam and Cushing[2] that a history of trauma is obtainable in high percentages of cases; (2) it is not possible either from the clinical or from the pathologic evidence to distinguish between the traumatic and the "nontraumatic" cases; (3) most pathologists do not consider the lesion to be an inflammation; (4) the source of a possible inflammation has never been found; (5) the accumulation of blood behaves like other hematomas in preformed cavities; (6) the late development of symptoms is explainable on the basis of osmosis[3]; (7) most subdural hematomas can be cured by simple removal of the fluid through a burr hole and a cure would not be likely if there were an active inflammatory process.

In the present series of 60 patients with chronic subdural hematoma there were 51 males and 9 females, whose ages ranged from 6 to 75 years (average 47 years). No infants are included because they usually present a different clinical picture. All were treated in the Department of Neurosurgery of the University Hospital in Copenhagen. Only 32 of the 60 patients gave a history of moderate to severe cranial injury (such as that occasioned by a fall from a ladder, a fall from a bicycle, a car accident), and in only 12 of these was the trauma so severe that the patient became unconscious. In 13 of the remaining 28 patients, the injury was very slight (such as that caused by a fall from a chair without actually striking the head, striking the head against a trunk door while lifting something from a car, a blow on the cheek from a schoolteacher). In the remaining 15 patients (25 per cent) it was impossible to trace a history of trauma.

Other authors [4,12] cite a high frequency of unknown cause of chronic subdural hematoma; thus, if one assumes that almost all subdural hematomas are caused by trauma, it seems reasonable to say that in many cases the injury may be very slight, similar to that experienced by all of us several times during our lives. Why only a few people sustain this type of hematoma after slight injury is still open to question, as no single antecedent factor common to all cases has been found. Virchow noted that the lesions were more common in insane than in sane persons. In the present series none of the patients was insane prior to the development of the hematoma; however, 48 of the 60 patients had rather severe psychic disturbance at the time of admission to the hospital. Chronic alcoholism is also believed to be a causal factor in the development of the lesion.[2] Twelve of the 60 patients were known to be addicted to alcohol. The significance of this high percentage is not entirely clear; however, alcohol addicts as well as insane persons are prone to sustain cerebral injury through irresponsible actions.

Symptomatology and Diagnosis

A latent interval of perhaps months from the occurrence of trauma, and slow development of symptoms is characteristic of chronic subdural hematoma. The long delay of symptoms contrasts with the delay of perhaps only hours that

usually follows bleeding into other intrabody spaces. This slow development was useful to Virchow in his recognition of "spontaneous" pachymeningitis. He and later authors attributed the progressive development of symptoms to repeated slight bleedings from the capillaries on the inner surfaces of the membranes; but such evidence never was found at operation or at necropsy; usually the gross content of the hematoma was perfectly homogeneous. Trotter[11] suggested that the development of the clinical picture was due to repeated bleeding from the responsible vessel; this theory likewise has not been proved. Some authors [13,14] suggested that the lesion was a neoplastic process.

Gardner's[3] explanation of the slow development of symptoms of chronic subdural hematoma has received general acceptance. According to Gardner the mechanism of the delayed appearance of symptoms is dependent on osmosis. He believes that the subdural space is anatomically unique: there is no lymphatic drainage; thus, when a blood clot is formed in the subdural space, it cannot be absorbed and it becomes surrounded by a semipermeable membrane. The colloidal-osmotic pressure draws fluid into the membranous sac and the hematoma becomes enlarged. Gardner experimented with cellophane sacs containing whole canine blood and found that when they were immersed in spinal fluid or placed in the subdural space in dogs, the contents of each sac increased in weight up to about 100 per cent within a few days. Zollinger and Gross [15] in their studies showed that disintegration of blood produced a slow rise in osmotic pressure.

The duration of the latent interval perhaps is correlated with the size of the hematoma or with the extent of the possible senile atrophy of the brain. In those cases of the series considered here in which it was possible to determine the age of the hematoma, the variation of the latent interval was from two weeks to eight months (average, nine weeks).

The symptoms of chronic subdural hematoma may be slight for a long time or they may be misleading or, as stated by Pette,[16] "pachymeningitis is found where it is not diagnosed, and diagnosed where it is not found." Characteristically, in contrast to most other intracranial lesions, chronic subdural hematomas cause more generalized symptoms. For example, whereas most tumors of the hemisphere, epidural hematomas, and acute subdural hematomas produce localizing neurological symptoms such as paresis, aphasia, anisocoria and spasticity, chronic subdural hematomas are more likely to produce what must be presumed to be generalized cerebral symptoms such as mental confusion, drowsiness, and psychosis. In this series, as stated, 48 of the 60 patients had severe psychic disturbance (Table 1) and 10 of these patients before their admission to the neurosurgical service were admitted to the Department of Psychiatry and a diagnosis of neurosurgical lesions was subsequently made, usually because of the development of papilledema. It therefore is wise to hesitate before making a diagnosis of chronic subdural hematoma in the patient who is completely alert and oriented.

Frequently one suspects the diagnosis on first meeting the patient: his appearance shows neglect of personal grooming and suggests mental derangement. Occasionally other lesions, such as glioblastoma multiforme, cause

similar signs. A history of trauma may help to establish the correct diagnosis, yet it must be kept in mind that slight injury often aggravates the symptoms of an intracranial tumor, and the patient is then likely to attribute all of his complaints to the trauma, forgetting that he had been feeling not completely well before it occurred.

The incidence of various symptoms in patients of this series is tabulated in Table 1. Headache, the most frequent complaint of the patients, usually was not severe but rather like a dull pressure. However, the headache can be very severe and without objective symptoms, as it was in a patient recently admitted to the Cleveland Clinic. He was completely alert and his only complaint was a headache so severe that it simulated neuralgia. In 27 cases the spinal fluid was examined and was normal in 11 cases—protein content was elevated in 16; the spinal fluid was xanthochromic in 7. The Wassermann reaction was positive in 2 of 19 specimens tested.

TABLE 1

Symptoms in 60 Patients Having Chronic Subdural Hematoma

Symptoms	Incidence, No. of Patients
Psychic disturbances	48
Headache	43
Papilledema	32 (of 58)
Neurological symptoms, localizing (paresis, aphasia, convulsions)	12
Vomiting	9

The frequently misleading nature of the symptoms is exemplified by the fact that the tentative diagnosis was correct in only half of the patients of this series (Table 2).

TABLE 2

Tentative Diagnoses in 60 Cases of Chronic Subdural Hematoma

Tentative Diagnosis		No. of Cases
Correct		30
Incorrect		27
Intracranial tumor	15	
Cerebral contusion	5	
Epidural hematoma	2	
Other	5	
Not recorded		3

Although both encephalography and angiography often will aid in verifying a tentative diagnosis of subdural hematoma, and either of the procedures may show the lesion, bilateral angiography seems to be the procedure of choice if a subdural hematoma is suspected. The diagnosis of a hematoma is more certain when the vessels are seen pressed back from the skull in an A-P angiogram than it is when a dislocation of the ventricular system is found in an encephalogram. Also, if the lesion is bilateral, the latter dislocation may be slight. In some cases only an oblique angiogram will be diagnostic, as the hematoma may be located anteriorly or posteriorly. The preoperative differential diagnosis between tumor and subdural hematoma is important, because the hematoma can be treated with evacuation through a burr hole, which is a simpler procedure than turning a skull flap as for a tumor.

Trephine often is used as a diagnostic procedure in cases of suspected subdural hematomas; but if the findings are negative, another diagnostic procedure usually will be necessary. If a subdural hematoma is present, the dura in most cases appears greenish or dark bluish at trephination. However, in one of the patients in this series in whom an epidural hematoma was suspected, the color appeared to be normal; hence, the dura was not opened and the outcome was fatal. It therefore seems advisable to open the dura in all cases of explorative burr holes.

Treatment and Results

When a subdural hematoma has been diagnosed, the only adequate treatment is surgical removal of the lesion. It usually is preferable to remove the hematoma through one or more trephines, and in the Clinic in Copenhagen it has been routine practice to make anterior and posterior burr holes. Quite often the lesion has been discovered through one of the parietal burr holes made for the purpose of ventriculography, and then that specific opening has been used therapeutically. The content of the chronic subdural hematoma commonly is a dark fluid that is easily evacuated by suction and washing with saline solution. However, if the hematoma is of more recent onset, it may be somewhat solid, and complete removal through a small burr hole may be difficult. Suction through a soft rubber catheter introduced into the subdural space may be helpful in those cases. It has been routine procedure in the Clinic in Copenhagen to try to open the inner membrane and the arachnoid in an attempt to drain the hematoma to the subarachnoid space. In the Cleveland Clinic[17] it is believed to be advantageous to try to distend the compressed brain by injecting saline solution through a lumbar puncture. If this is done, the arachnoid at the site of the burr hole should not be opened, as the fluid may escape. Usually there is only slight bleeding on evacuation of a chronic subdural hematoma; however, as the removal of the hematoma may not always be complete, a rubber drain is left in each burr hole for about 48 hours.

In our series, if the correct diagnosis could not be established either by the clinical examination or by the roentgenographic studies, the preoperative

diagnosis often was intracranial tumor, and in those cases a skull flap was turned down and complete removal of the membranes often was possible. The amount of membrane removed does not seem to be a factor in the patient's recovery, the postoperative courses after minimal removal comparing favorably with those following removal of most of the membrane when a skull flap was turned down. The cerebral cortex frequently appeared dehydrated, as described by Christensen.[18] Other authors[5] found at autopsy that there appeared to be edema of the underlying cerebral tissue.

Of the 60 patients in this series, 12 died (9 during hospitalization and 3 following discharge from the hospital). At the time of follow-up, of the remaining 48 patients 30 were without complaints and doing very well; 5 had several minor complaints but the results were considered to be good; 10 had various degrees of incapacity (some could not do their former work); 1 was completely deranged mentally; and 2 could not be traced.

At the time of follow-up, the most common complaints were headache, impairment of memory, and fatigue. A few patients had slight paresis, which in some was homolateral with the hematoma.

A surprisingly long time elapsed after surgery until the patients in the two best groups were completely well—an average of seven months. The interval of time was especially long for the elderly patients.

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FIFTY PER CENT UROKON SODIUM* AS AN INTRAVENOUS UROGRAPHIC CONTRAST MEDIUM

A Study Based on 250 Cases

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INTRAVENOUS urography is a safe, relatively simple procedure that offers much valuable information about the form and the functioning of the urinary tract and its neighboring structures. For these reasons it frequently is employed as a diagnostic measure. Although several commercially available contrast media give good visualization of the urinary tract and cause few postinjection reactions, new preparations constantly are being sought which will improve visualization and further decrease the likelihood of untoward reactions.

The medium that we have been testing, Urokon sodium (sodium 3-acetylamino-2,4,6-triiodobenzoate), is a brand of sodium acetrizoate. The dry salt is a white crystalline powder that is soluble in water. Urokon sodium has been thoroughly investigated both as a 30 per cent and as a 70 per cent solution and has been found to be satisfactory as a contrast medium. It now is commercially available as a 50 per cent solution. Because of the higher concentration of iodine, visualization of the urinary tract should be better than with the 30 per cent solution. Fifty per cent Urokon contains 65.8 per cent iodine by weight, which is more iodine than is in Hypaque (59.8 per cent), in Diodrast (48.9 per cent), or in Neo-Iopax (51.5 per cent).

Procedure

A series of 250 consecutive ambulatory outpatients were used in this study. There were 147 males and 103 females who were from 11 to 80 years of age and from 76 to 305 pounds in weight.

A *urogram survey sheet* was made out for each patient who was sent to the Department of Roentgenology for urographic study. On the sheet were recorded the patient's Clinic number, age, race, weight, and sex. The common allergies and those reactions most frequently seen following injection of urographic contrast media were listed on the survey sheet, and a history of these was noted prior to injection of the medium. On the same survey sheet were later recorded the length of time allowed for injecting the Urokon, the presence of any post-injection reactions experienced by the patient, and the rating of the urograms for diagnostic quality.

**The Urokon sodium used in this study was kindly supplied by Mr. B. A. Parker of Mallinckrodt Chemical Works, 3600 N. Second St., St. Louis 7, Mo.*

The urographic series for each patient consisted of five films, the first two of which were exposed 5 and 15 minutes, respectively, after injection of the medium, with abdominal compression in place. The compression was then removed and 16- and 30-minute films were exposed. A 30-minute film centered over the bladder area also was made.

Reactions

Twenty-three (9.2 per cent) of the 250 patients gave a history of previous allergies, enumerated as follows: hay fever, 11; asthma, 3; food allergy, 3; drug allergies, 4; hives and eczema, 1 each. Of those 23 patients, 15 had one or more reactions to the injection of 50 per cent Urokon. Of the 227 patients without known allergies, 111 (approximately 50 per cent) had one or more reactions to the medium. Thus, there was a total of 126 (50.4 per cent) patients who had one or more reactions to 50 per cent Urokon. Table 1 gives an analysis of reactions; those most frequently experienced were nausea, vomiting, and bad taste. Although all were unpleasant, none of the reactions were serious and all promptly subsided without treatment.

TABLE 1
Reactions to 50 Per Cent Urokon Sodium in 126 Patients

Reaction	Incidence
Nausea	67
Bad taste	47
Vomiting	25
Warmth	17
Dizziness	4
Sneezing	3
Flushing	2
Moderate pain	1
Choking	1
Tinnitus	1
Edema (eyelids)	1

Ninety-one patients were given injections over periods of one minute each, and 49 (54 per cent) of these had reactions. Of the remaining 159 patients who were given injections over periods of two minutes each, 77 (48.4 per cent) had reactions. A comparison of these figures indicates that there apparently is no great advantage in using the slower rate of injection.

Diagnostic Rating of Urograms

The technical quality of the urograms was rated according to the criteria devised by Hoppe[1]; both the demonstration of morphologic structure of the urinary tract and the density of the shadows were taken into consideration (Table 2). In general the results were good. Ninety-four urograms (37.6 per

cent) were rated excellent with brilliant shadows, and 113 (45.2 per cent) were rated good.

TABLE 2

Analysis of Urographic Visualization with Urokon Sodium in 250 Patients*

	No. of patients	Per cent of total
A. Morphology of upper urinary tract		
No visualization	0	0
Upper third of either or both ureters faintly visible	4	1.6
Upper third of either or both ureters distinctly visible	6	2.4
Calyces, pelvis and upper ureter of one side visible	17	6.8
Calyces, pelvis and upper ureter distinctly visible on one side with partial visualization on other side	58	23.2
Calyces, pelves and upper ureters of both sides distinctly visible	165	66.0
Total	250	100.0
B. Only the bladder visible	0	0
C. Radiographic quality (density of shadows)		
No visualization	0	0
Poor—shadows barely visible, morphology indistinct	12	4.8
Fair—faint but distinct outlines	31	12.4
Good—distinct shadows of unquestionable diagnostic quality	113	45.2
Excellent—brilliant shadows, structures stand out in bold relief in contrast to surrounding tissue	94	37.6
Total	250	100.0

The excretion of Urokon was prompt as evidenced by the fact that the best concentration of the medium in the upper urinary tract was usually seen on the 5- or 15-minute films in each series. In 118 cases the 5-minute films showed the best concentration; and in 122 cases the concentration was best on the 15-minute films.

Comparison with Hypaque

Root and Strittmatter[2] recently reported the findings in a series of 350 patients in whom Hypaque was used as the urographic medium. The urogram survey sheets were of the same form as those used in the present study of Urokon. Only 9.7 per cent of the patients receiving Hypaque exhibited any reaction, as compared with the 50.4 per cent who had reactions to injections of 50 per cent Urokon. Visualization of the urinary tract was slightly better with Hypaque: 43.4 per cent showed excellent contrast with brilliant shadows as compared to 37.6 per cent with 50 per cent Urokon. Because of the significantly

**Criteria according to Hoppe.*[1]

lower percentage of patients having reactions, in addition to the good visualization achieved, Hypaque has become our choice of medium for intravenous urography.

Summary

Intravenous urograms, for which 50 per cent Urokon was used as a contrast medium, were made for a series of 250 Clinic patients. Visualization of the urinary tract was good. The incidence of postinjection reactions (50.4 per cent) was high, although no reactions of a serious nature were encountered. In comparison with 50 per cent Urokon, Hypaque[2] caused fewer postinjection reactions (incidence, 9.7 per cent) and provided slightly better visualization of the urinary tract.

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TREATMENT OF CANCER OF THE THYROID WITH DESICCATED THYROID

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IN recent years it has been discovered that certain types of goiter diminish in size when patients are given desiccated thyroid. Many large goiters resulting from struma lymphomatosa shrink or even disappear when thyroid is given in doses of 2 to 4 grains daily.[1] Some adenomas of the thyroid and some multinodular goiters get smaller.[2] Now it appears that some well-differentiated cancers of the thyroid also can be controlled by thyroid feeding.

Small doses of thyroid, up to two grains daily, do not appear to have any significant effect upon goiters or cancers. It is necessary to give a full replacement dose of three to four grains daily to obtain favorable results. Presumably such doses of desiccated thyroid furnish so much exogenous thyroid hormone that it is no longer necessary for the thyroid gland to function. The exogenous hormone suppresses the formation of the thyroid-stimulating hormone of the pituitary; and the thyroid, deprived of pituitary stimulation, atrophies. Similar dependency on hormones has been observed in certain cancers of the prostate and breast.

My interest in the dependency of thyroid tumors on pituitary hormones was first awakened eight years ago when I saw a woman with severe hyperthyroidism and an oxyphilic adenocarcinoma (Hürthle cell cancer) of the thyroid that had metastasized to the lungs. Serial roentgenograms of this patient's lungs obtained during the preceding two years showed no increase in the size of the metastatic nodules; in fact, some of them seemed to be getting a little smaller.

I erroneously assumed that the patient's hyperthyroidism was being caused by the cancer, and began treatment with radioactive iodine. Soon the hyperthyroidism was controlled and the patient developed signs of myxedema. At this point the metastatic tumors began to enlarge rapidly, and a few months later the patient died.

In retrospect, it seems clear that the hyperthyroidism had been caused not by the cancer but by hyperfunctioning nonmalignant thyroid tissue. Presumably, the excessive thyroid hormone had suppressed the output of thyroid-stimulating hormone of the pituitary, and this suppression had resulted in an arrest of the growth of the tumor. As soon as the function of the thyroid was destroyed, the resultant deficiency of circulating thyroid hormone stimulated the pituitary. It was the increased output of thyroid-stimulating hormone from the pituitary, that made the cancer grow.

During the next few years I saw several more examples of differentiated thyroid cancers that blossomed and grew rapidly when myxedema had been induced by I^{131}. The trend of the tumor's growth was promptly reversed when desiccated thyroid was given in doses of three to four grains daily. I now have

A. Metastasis of papillary carcinoma of thyroid to both lungs, most marked in lower lobes. B. (The same case as shown in A.) Roentgenogram taken after four years of treatment with 3 grains of desiccated thyroid daily. No evidence of metastatic carcinoma.

followed five patients with pulmonary metastases of papillary carcinoma treated with desiccated thyroid for from one to five years, and in every case there has been cessation of growth of the carcinoma, as evidenced by improvement in the roentgenographic appearance of the chest or complete disappearance of the tumors both in the neck and in the chest (Figure). Similar results have been reported in England by Balme.[3] In two other cases with solitary metastases in bone, there were apparent arrest of the cancer's growth for from one to five years and recalcification during treatment with thyroid and roentgen therapy.

Discussion

For the past three years I have made it a practice to give two to four grains of desiccated thyroid daily to all patients who have had operations for cancer of the thyroid. Since the course of this disease may be extremely slow it is difficult to assess the results. All that can be said at the present time is that there have been no favorable responses to thyroid feeding in patients with highly malignant or undifferentiated cancers of the thyroid. On the other hand, there have been no recurrences of tumors of low malignancy treated with desiccated thyroid even in patients who had only partial removal of extensive papillary carcinomas.

It will take many years to estimate the value of desiccated thyroid in the treatment of low-grade cancers of the thyroid. In the meantime the treatment is inexpensive, harmless, and certainly worth further trial.

To aid in determining the value of treatment with desiccated thyroid in these rare cancers, it would be helpful if those who have had experience with this method would send me summaries of their cases, together with representative slides of the cancers. In this way perhaps we can determine what types of cancer will respond favorably to endocrine therapy.

Summary

Feeding desiccated thyroid in doses of three to four grains daily appears to arrest the growth of papillary carcinomas of the thyroid. In some cases under treatment metastatic nodules in the lungs have disappeared.

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A STUDY OF THYROID FAILURE FOLLOWING RADIOIODINE* THERAPY FOR GRAVES' DISEASE

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THE use of radioactive iodine as a treatment of choice for the hyperthyroidism due to Graves' disease is being increasingly accepted. However, in some patients one consequence of the use of radioiodine, I^{131}, has been the occurrence of permanent thyroid failure. The purpose of this study is to review the circumstances of thyroid failure as a complication of radioiodine therapy in a series of patients having Graves' disease, in order to evaluate factors that may affect the incidence of that complication.

Method of Study and Treatment

Three hundred and thirty-two patients with Graves' disease were treated with radioiodine at Cleveland Clinic between January 1952 and June 1954. The patients constituted five groups (A,B,C,D,E) corresponding to the five physicians who prescribed treatment for them. Two physicians used the same method of calculating the dosages, and the other three each based their estimates of dosage on clinical judgment. Doses for groups A and B were calculated on the basis of estimated weight of the thyroid gland and the initial I^{131} uptake in comparison with tracer studies. The following formula was used to calculate the dose in an attempt to deliver 100 microcuries per gram of gland (normal weight taken as 25 grams) unless the patient had a goiter larger than 75 grams or had symptoms of cardiac failure or angina pectoris, or severe disabling hyperthyroidism, when 150 to 200 microcuries per gram was given.

$$\frac{\text{Estimated weight of gland (Gm.)} \times \text{microcuries/Gm.} \times 100}{\text{Per cent tracer uptake}} = \frac{\text{Microcuries } I^{131}}{1000} = \text{Millicuries } I^{131}$$

*The radioactive iodine used in this investigation was supplied by the Abbott Laboratories on authorization from the Isotopes Division, U. S. Atomic Energy Commission, Oakridge, Tennessee.

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If two months after the initial dose of I^{131} the patient was definitely improved but still hyperthyroid and the I^{131} uptake was normal or high, an additional dose, calculated by the above method, was administered. However, if the I^{131} uptake was low (below 15 per cent) in that type of patient, no further I^{131} was given until two more months had elapsed. If the patient was unimproved after the first treatment, a dose of 150 or 200 microcuries per gram was administered. (I^{131} uptakes were measured at the end of 24 hours in the patients of this series.)

The chief concern of all the physicians was to control the hyperthyroidism as quickly as possible; the lesser concern was to try to control the incidence of subsequent thyroid failure.

After the initial dose of I^{131}, patients were seen at two-month intervals until they were euthyroid, and then again two months afterward. If thyroid failure had occurred, there was further observation. The diagnosis of thyroid failure was based upon various typical clinical and laboratory findings: symptoms of hypothyroidism (fatigue, cold intolerance, hoarseness, drowsiness); dry skin, puffiness of the eyes and face, gain in weight, and sluggish reponse of Achilles reflex; posttherapeutic I^{131} uptake (after tracer doses) below 15 per cent of that administered; basal metabolic rate of less than minus 20 per cent with some favorable response to desiccated thyroid treatment; and, usually, plasma cholesterol levels higher than normal.

Follow-up studies were made of some patients with thyroid failure by requesting them to return for examination after discontinuance of the use of desiccated thyroid. Questionnaires were sent to those who could not return, and to a few in whom thyroid failure was doubtful (a total of 42 patients) asking them whether they still were taking desiccated thyroid. Of the 38 patients who replied, 29 stated that they still were taking desiccated thyroid. Those patients who still were taking desiccated thyroid were regarded as having permanent thyroid failure, even though some may have regained normal thyroid function. Those who had discontinued taking desiccated thyroid and who felt well without it were regarded as having had temporary hypothyroidism.

TABLE 1

Analysis Of Results in 332 Cases of Graves' Disease After Radioiodine Therapy

Factor	No. patients treated per year			Series total	Percentage of series total
	1952	1953	1954 (first 6 mo.)		
Yearly total	135	119	78	332	100%
Temporary thyroid failure	3	2	2	7	2.1%
Permanent thyroid failure (percentage of yearly total)	16(11.7%)	9(7.5%)	7(8.9%)	32	9.6%

Results

Incidence and age distribution. Of 332 patients with Graves' disease treated with radioiodine therapy, 32 were classified as having permanent thyroid failure, an incidence of 9.6 per cent; and seven or 2.1 per cent were classified as having had temporary thyroid failure (Table 1). The ages of the patients were from 14 to 65 years.

Weight of thyroid gland. The estimated weights of the toxic thyroid glands before treatment were from 25 to 150 grams. The estimated weights of the toxic thyroid glands of the 32 patients who developed permanent thyroid failure were from 25 to 100 grams before treatment.

Duration of treatment. More than 90 per cent of the patients were euthyroid within four months following radioiodine therapy; most were definitely improved, if not euthyroid, within two months following radioiodine therapy. The average interval between the date of the last treatment of I^{131} and onset of thyroid failure was 3.7 months (2 to 6 months) (Fig. 1). In two patients (5 per cent) thyroid failure occurred six months after treatment.

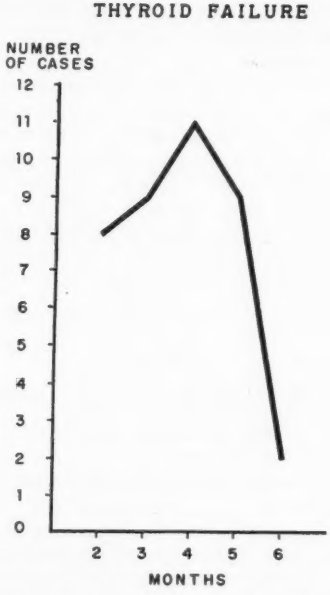

Fig. 1. Thyroid failure in 39 patients, as related to number of months it occurred after last dose of radioiodine.

Size of dose. Doses that produced euthyroidism varied from a single dose of 3 millicuries to multiple doses totaling 75 millicuries. Doses that produced thyroid failure varied from a single dose of 4 millicuries to multiple doses totaling

59 millicuries. The largest single dose producing hypothyroidism was 20 millicuries. Of the 39 patients who developed permanent or temporary thyroid failure, 31 had received single doses of I^{131}; 6 had received two doses of between 5 and 25 millicuries per dose; and 2 patients had received three doses respectively totaling 24 and 59 millicuries.

Temporary thyroid failure. Of the seven patients (2.1 per cent) who developed temporary thyroid failure, five had received single doses of 5 to 10 millicuries of I^{131}; two patients had received two doses totaling 13 and 43 millicuries respectively. All patients in whom thyroid failure was temporary required desiccated thyroid for periods of 3 to 21 months. Subsequently all discontinued the thyroid medication and since have been euthyroid for periods of 2 to 22 months.

Our observations indicate that in a small number of patients the thyroid gland may regain its function after there has been a hypothyroid state. It is possible that some patients who at the present time are considered as having "permanent" thyroid failure eventually will recover thyroid function. Figure 2 illustrates the course in a patient with this temporary thyroid failure due to I^{131}.

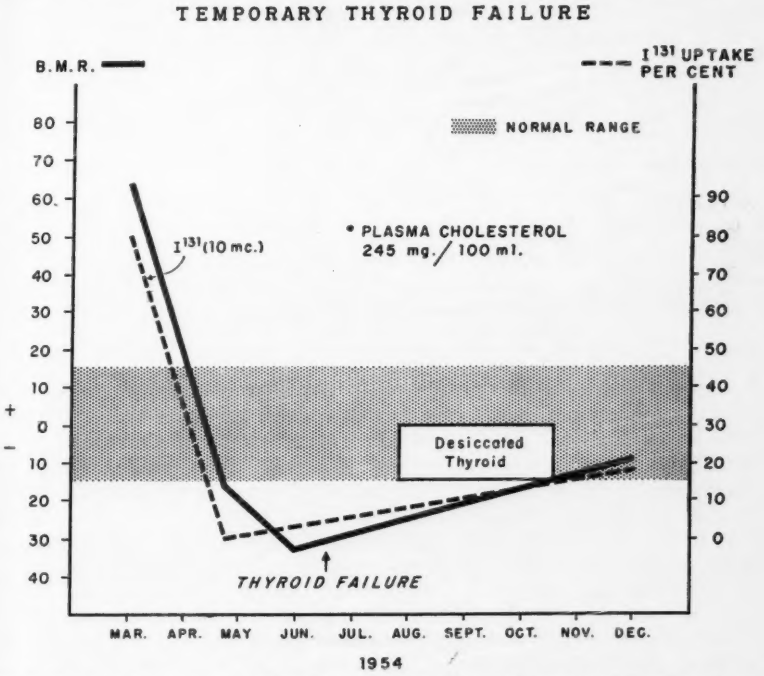

Fig. 2. Chart of data of a case of Graves' disease in a 39-year-old man who was treated with 10 mc. of I^{131}. Thyroid failure occurred four months after administration of radioiodine. He was treated with desiccated thyroid for three months, became euthyroid and remained so after discontinuance of thyroid therapy.

Permanent thyroid failure. Thirty-two patients had permanent thyroid failure and 26 of these were taking desiccated thyroid in doses of 30 to 240 mg. daily. This information was obtained from follow-up questionnaires or from the patients directly who were seen recently. The remaining six patients who were given desiccated thyroid for hypothyroidism, presumed permanent, did not return or reply to the questionnaire. Five of the 32 patients discontinued using desiccated thyroid temporarily and the symptoms of hypothyroidism recurred.

It is of interest to note that the incidence of permanent thyroid failure was lower in the two groups of patients whose doses of I^{131} were calculated on the basis of the weight of the gland (4.4 and 8.5 per cent) than in the other three groups of patients whose doses were based on clinical judgment (13.1, 14, 14.8 per cent) (Table 2).

TABLE 2

Analysis of Results in 332 Cases of Graves' Disease After Radioiodine Therapy

Factor	Number of patients in group					Series total	Percentage of series
	A (Dosage calculated)	B (Dosage calculated)	C (Dosage based on clinical judgment)	D (Dosage based on clinical judgment)	E (Dosage based on clinical judgment)		
Total number	113	70	38	57	54	332	100%
Temporary thyroid failure	2	3	1	1	0	7	
Permanent thyroid failure (percentage of group total)	5(4.4%)	6(8.5%)	5(13.1%)	8(14.0%)	8(14.8%)	32	9.6%

Before any symptoms or signs of thyroid failure were evident, an early laboratory clue as to the likelihood of its occurrence was a low I^{131} uptake. However, a number of patients who had low I^{131} uptakes and euthyroidism did not develop thyroid failure subsequently. The presence of a normal or high I^{131} uptake after the euthyroid state was attained, usually but not always indicated that the patient was not likely to develop thyroid failure.

Figure 3 summarizes the typical course of a patient who developed permanent thyroid failure after radioiodine therapy and who since has been taking desiccated thyroid.

Discussion

In a series of 1720 cases from the literature, Seed and Jaffé[1] reported that hypothyroidism of a more or less persistent nature occurred in 9 per cent of the patients treated with radioactive iodine. Chapman and associates[2] reported an

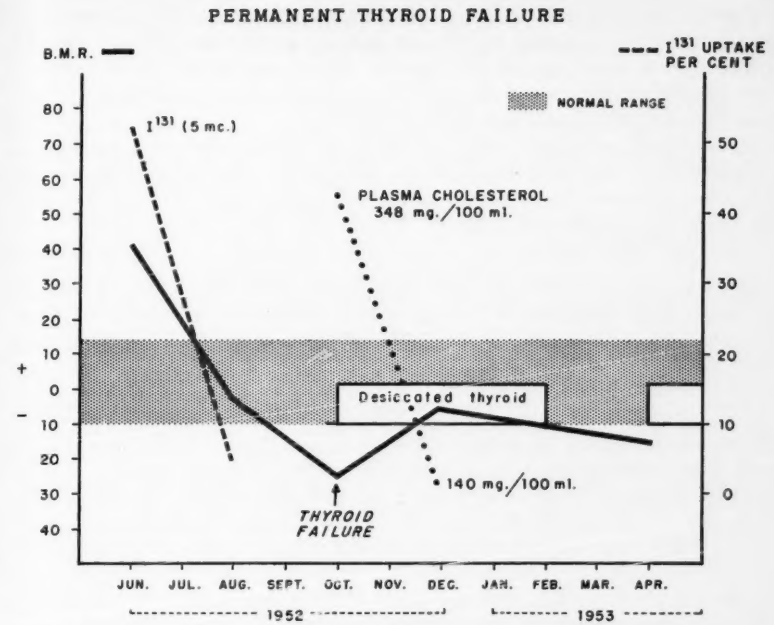

Fig. 3. Chart of data of a case of Graves' disease in a 49-year-old woman who developed a diffusely enlarged thyroid gland (estimated weight 30 Gm.). She was treated with 5 mc. of I^{131} and became euthyroid two months later. Four months after treatment, thyroid failure was evident. Desiccated thyroid was given for four months, and the patient became euthyroid again; treatment was then discontinued for two months and all symptoms of hypothyroidism recurred. Desiccated thyroid therapy was reinstituted, and two and one-half years later the patient still required it to remain euthyroid.

8 per cent incidence of posttreatment myxedema. The incidence of thyroid failure after surgical managemant of hyperthyroidism varies considerably within the individual series. Bartels[3] reviewed several series of surgical cases and found an incidence of hypothyroidism varying from 2.9 to 21 per cent. The latter finding was reported by Crile and McCullagh[4] for radical surgery of the thyroid gland in Graves' disease. They also reported that hypothyroidism occurred in 4.5 per cent of the cases involving conservative surgery. The incidence in Cattell's[5] series varied between 4 and 6 per cent. The incidence of the complication of thyroid failure increases with more radical subtotal thyroidectomy. We have observed the occurrence of thyroid failure in patients years after they had had partial thyroidectomy for Graves' disease, just as undoubtedly will occur years after I^{131} therapy. One of our patients, not included in the series reported here, was treated in 1949 with I^{131} and developed thyroid failure six years later.

There are several factors that apparently affect the incidence of thyroid failure. Overestimation of the dose of I^{131} is one important factor. After studying

the effect of radioiodine in the thyroid gland, Dailey and associates[6] suggested that lymphocytic infiltration, fibrosis, and moderate and diffuse follicular atrophy result from internal irradiation. They noted a higher incidence of lymphocytic infiltration and fibrosis in the thyroids of patients treated with I^{131} than in those patients untreated before surgery.

In our series the smaller the goiter the more likely was the patient to develop thyroid failure. This may be related to difficulty in estimation of dosage, but size alone may be a factor. Previous observations indicate that the larger the goiter the more resistant it is to I^{131}.[7]

The age of the patient was of no etiologic significance.

Perhaps the most important factor is the, as yet unexplained, variation in sensitivity of the thyroid cells in the goiters of different patients to the effects of radiation, despite identical clinical and laboratory findings and the same-sized doses of I^{131}; thus, one patient may develop thyroid failure and another continue to have hyperthyroidism.

It may be that a variation in the duration of retention of I^{131} in the thyroid gland may partially explain this difference in sensitivity, but we have no data verifying or refuting this possible explanation. The histopathologic structure of the hyperplastic thyroid gland before treatment with I^{131} may also be a partial explanation for the variation in sensitivity to I^{131} and occurrence of thyroid failure. We, and others[8] before us, have observed that the thyroid glands of some patients having Graves' disease show focal areas of thyroid cells with oxyphilia in the cytoplasm, which are associated with varying degrees of lymphocytic infiltration and fibrosis; this condition has been called thyroiditis, but we believe it represents focal cellular exhaustion consequent to the stress of overactivity of the cells. This histopathologic condition is observed in only a small percentage of patients with Graves' disease, but the incidence of postoperative thyroid failure is known to be very high in this group.[3,8] Thus, focal thyroid cell exhaustion occurring prior to treatment with radioiodine may be another part of the explanation for the variation in sensitivity to I^{131}. There probably are unknown mechanisms that also may explain this variability in sensitivity to I^{131}.

Summary

Of 332 patients with Graves' disease treated with radioactive iodine, 32 (9.6 per cent) developed permanent thyroid failure. Temporary thyroid failure occurred in 7 patients (2.1 per cent). The incidence of thyroid failure was lower when the I^{131} dosages were calculated on the basis of estimated weight of the thyroid gland than when based on clinical judgment alone. The thyroid failure usually occurred within two months after the patient had become euthyroid. The occurrence of low I^{131} uptake after the patient became euthyroid was often a forewarning of the development of thyroid failure.

Factors that predisposed the development of thyroid failure were overdosage of I^{131}, small size of goiter, and variation in sensitivity of the thyroid cells to I^{131}.

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PRELIMINARY OBSERVATIONS ON HEMIGASTRECTOMY WITH SUBDIAPHRAGMATIC VAGOTOMY FOR THE AVERAGE CASE OF CHRONIC DUODENAL ULCER

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ABOUT two years ago, it became clear to my colleagues and me that subdiaphragmatic vagotomy with posterior gastroenterostomy was not a completely satisfactory answer to the problem presented by the patient with a "surgical" duodenal ulcer (one for which surgery is indicated). At that time studies showed that 5 per cent of patients followed at least five years required a second operation for ulcer. Although the procedure has a very low mortality rate —in our experience less than one-half of one per cent—the rate of failure seemed too high for us to continue performing this operation for the average elective case. Accordingly, we decided to change to subdiaphragmatic vagotomy with hemigastrectomy. This promised a more reliable relief of the ulcer diathesis, yet preserved enough stomach to avoid most of the ills common to the post-gastrectomy state. However, in an effort to maintain a low mortality rate, comparable to that of the simpler operation, we also decided to continue to do vagotomy with posterior gastroenterostomy in those patients whose condition was such that it seemed that gastric resection would appreciably increase the surgical risk. About four of every five vagotomized patients have had a partial resection since this policy was started, and the other one of every five, a gastroenterostomy.

Although many years will have to pass before the program can be finally evaluated, definite impressions already have been gained. Since this program was adopted there has been no evidence, clinical or otherwise, of recurrent ulceration in any of our 120 patients who had hemigastrectomy with vagotomy. These findings are consistent with those of surgeons who have had wider experience with vagotomy with hemigastrectomy.

So few patients have lost weight or have been unable to gain weight after vagotomy and hemigastrectomy that apparently in this regard results of this operation will be comparable to the similarly favorable results following vagotomy and posterior gastroenterostomy. Other side effects such as diarrhea, or the "dump" syndrome likewise have proved uncommon. But the record as regards operative mortality is not as good. During the last year two patients died in the immediately postoperative period following hemigastrectomy with vagotomy. These were the first deaths after operations for chronic duodenal ulcer since 1950, the year when vagotomy with posterior gastroenterostomy became the standard procedure on my service. The patients were relatively young men (48 and 34 years old), and both had had severe, penetrating duodenal ulcers.

The first patient died of a coronary thrombosis proved at autopsy; the second died of hemorrhagic pancreatitis that, at autopsy proved to be unrelated, in continuity at least, to the turn-in of the duodenal stump. One cannot be certain of the relationship between the resections and the fatal complications but, in the case of the patient who had hemorrhagic pancreatitis it is fair to assume that he might have lived if the lesser procedure of gastroenterostomy had been substituted for the gastric resection. These two operative fatalities yield a mortality rate for vagotomy and hemigastrectomy in this personal series of 61 cases of about 3 per cent. This contrasts with no postoperative deaths among 123 patients who had vagotomy with posterior gastroenterostomy.

Comment

The early results of vagotomy and hemigastrectomy in selected cases appear to be fairly good—with the exception of two operative fatalities neither of which was necessarily related directly to the resection itself. It is gratifying to note the absence so far of recurrent ulceration, but a long-term study is needed to include possible late recurrences. The low incidence of severe side effects is probably definitive, since these in general appear promptly after operation. It would seem that vagotomy with hemigastrectomy is not as incapacitating to bodily economy as is a radical gastric resection.

Although these early results may be described as encouraging, late results may affect the final conclusions. For example, we may ultimately come to the decision that vagotomy and posterior gastroenterostomy—with a calculated chance of about 5 per cent for secondary gastric resection—is the best procedure for the average case of chronic duodenal ulcer. Or, we may become so skillful in predicting the likelihood of recurrent ulceration, that a partial gastric resection will be required only in a minority of patients with duodenal ulcer.

BILATERAL THROMBOSIS OF THE INTERNAL CAROTID ARTERY

Report of Three Cases

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SINCE the advent of intracranial angiography the remarkable compensatory capacity of the circle of Willis has been demonstrated in various vascular disorders of the cerebral circulation and particularly in cases of unilateral thrombosis of the internal carotid artery. That patients with bilateral occlusion of this artery could develop collateral circulation sufficient to prevent severe paralysis, blindness and a global aphasia has not been heretofore regarded as a possibility.

It is the purpose of this paper to present case reports of three patients with bilateral thrombosis of the internal carotid artery and to outline some of the clinical features of this condition.

Numerous cases of unilateral thrombosis of this vessel have been reported since arteriography established this circulatory defect as a clinical entity.[1,2,3] The clinical diagnosis in the majority of these cases has been neoplasm, with subdural hematoma or multiple small vascular lesions as secondary considerations. The greatest incidence has been between the ages of 30 and 60 years. Etiologic factors such as thromboangiitis obliterans, syphilis, blood dyscrasias, acute infections and trauma to the neck have been suggested, but in a large autopsy series described by Fisher[1] the cause was found almost without exception to be atherosclerosis.

Early recognition of thrombosis of the internal carotid artery is the exception rather than the rule. The characteristic syndrome of monocular optic atrophy, contralateral homonymous hemianopsia, hemisensory defects and complete hemiplegia is very rarely found. Aphasia, psychiatric disturbances, headaches, visual-field defects and a slowly progressive course are signs that may be associated with the lesion but hardly are considered pathognomonic of either unilateral or bilateral thrombosis.

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The symptoms and signs produced by bilateral occlusion depend on the extent of functioning collateral circulation and the rapidity of onset of the obstruction. The collateral circulation[4] by way of the external carotid artery may be through the external maxillary artery and the external angular artery of the eye to the ophthalmic artery, via anastomoses between the temporal and supra-orbital arteries to the ophthalmic, and by means of intracranial branches of the middle meningeal to the lacrimal and nasociliary arteries, these being branches of the ophthalmic. There is in addition some circulation existing from one side to the other across the midline of the face, oral cavity and scalp. Walsh and Smith[5] state that homolateral blindness is rare with thrombosis of the internal carotid artery because it requires extension of the process into the retinal artery and the excellent collateral circulation in the retrobulbar tissues usually prevents such an involvement. In addition the contribution of the posterior circulation from the basilar artery to the posterior cerebral arteries, to the posterior communicating and posterior choroidal vessels is of great importance, as well as are the smaller communicating channels of the cortex. The usefulness of the anterior communicating artery naturally depends on its capacity and supply from the side having the better volume flow.

Frøvig[6] reported in detail a case of bilateral thrombosis of the common carotid artery in a 20-year-old girl in whom a vertebral artery was hypertrophied and supplied blood to the anterior cerebral vessels, as was demonstrated by angiography. The patient was alive at the time of the report, and resected segments of the carotids revealed complete obstruction, the process being regarded as thromboangiitis obliterans.

Perhaps the most significant report pertaining to thrombosis of the internal carotid artery is that of Miller Fisher.[1] In a series of 432 autopsies, complete occlusion of one artery was present in 34 and of both arteries in 11. In a review of the histories of these cases the most commonly encountered clinical sign was hemiplegia that developed over one or two days. Signs of cerebral neurologic defect were absent in seven cases of unilateral occlusion, but none of those with bilateral occlusion was free of symptoms. Johnson and Walker[2] in a review of 107 cases (their own and others) of unilateral thrombosis found hemiplegia or hemiparesis in 80 per cent of the cases. The disease was associated with transient episodes of motor or sensory defects in about 40 per cent of the cases and the thrombosis occurred on the left side in 65 per cent.

CASE REPORTS

Case 1. A 44-year-old woman was seen in January, 1955, with a history of illness beginning in May, 1954, when she developed a sudden episode of paraplegia from which she recovered within a few hours. In October, 1954, she developed mental symptoms for which she received electric coma therapy. The mental changes consisted of impairment of memory, inattention and hallucinations. She had headaches, right eye soreness, bilateral numbness of the lower half of the face; apraxia and astereognosis. She complained of a constant odor and blurring of vision. An anomic aphasia and alexia existed. Urgency, frequency and urinary incontinence were present.

The patient was obese with a blood pressure of 170/105. The external ocular movements were normal and without nystagmus. The right pupil was larger than the left. Light and accommodation reactions were normal. Confrontation testing revealed a right homonymous hemianopsia. The retinal veins were prominent but no papilledema was present. There was no sensory or motor weakness of the face. Gait was slow but otherwise normal and no paresis was present. There was hypalgesia in the right arm and leg. Deep pressure and touch sensations were preserved. The biceps, triceps and radial reflexes were hyperactive on the left, while the patellar and Achilles reflexes were increased on the right, and a right ankle clonus was present. The abdominal reflexes were intact. The Babinski, Gordon and Oppenheim signs were absent but the Hoffman was markedly positive bilaterally. Aphasia both receptive and expressive; agraphia, astereognosis, and apraxia of the right hand were demonstrated. In performing the finger-to-nose test there was pronounced tremor in the left hand and to a lesser extent in the right. The patient was unable to perform the heel-to-knee test adequately with either leg. The Holmes rebound phenomenon was present bilaterally. The buccal or snout reflex was not positive.

Routine laboratory studies and roentgenograms of the skull and chest were normal. On February 2, 1955, the patient was taken to surgery and bilateral carotid arteriography was performed under Pentothal anesthesia. Thrombosis of the internal carotid arteries was demonstrated immediately above the bifurcation of both common carotids. Filling

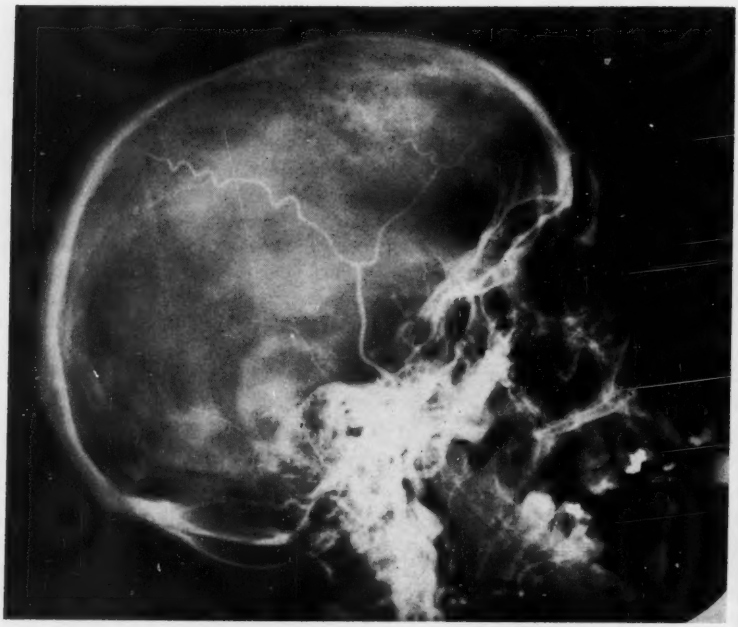

Fig. 1. (Case 1). Left carotid arteriogram showing absence of filling of the internal carotid artery and only a slight amount of contrast medium in its siphon. Collateral circulation by way of the left ophthalmic artery could not be clearly demonstrated.

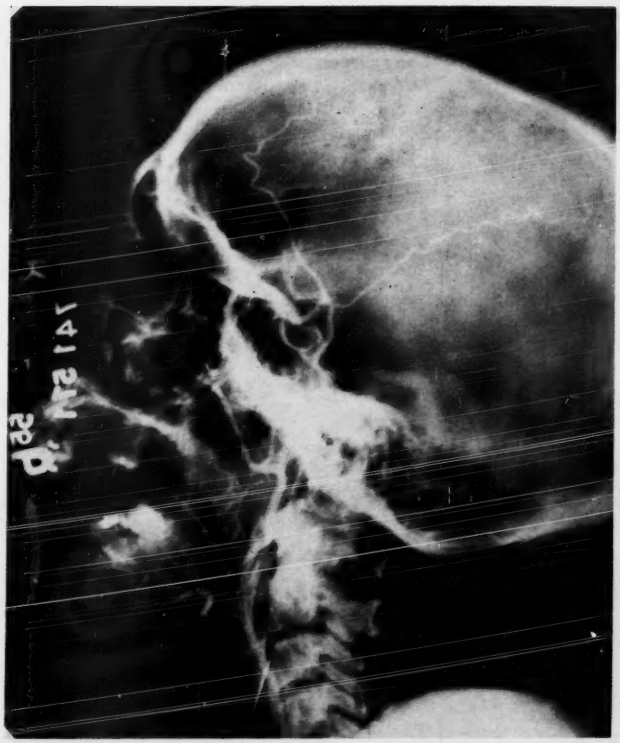

Fig. 2. (Case 1). Right carotid arteriogram showing occlusion of the right internal carotid artery but a well-defined siphon. The ophthalmic artery can be recognized as a fine line in the retrobulbar region.

of both internal carotid arteries was demonstrated in the siphons particularly on the right side and both ophthalmic and external carotid arteries contained contrast medium (Figs. 1 and 2). Bilateral cervical sympathectomy was performed, at which time both internal carotid arteries were found to be firm, nonpulsating, hard, gray-white cords.

Postoperatively the patient responded readily but it was noted that she had developed pronounced weakness of the right arm and leg which had not been present on admission. The deep tendon reflexes were unchanged but a Babinski sign was now present on the right. The patient was discharged from the hospital on February 8; four months later she was seen as an outpatient and there was no progression of her symptoms nor change in the neurologic picture.

Case 2. A 55-year-old man was first seen on April 11, 1955, complaining of unsteady gait, weakness in the right leg and "spells" for two years. In November, 1953, he developed a severe occipital headache and retired to bed. His wife noted thick speech and weakness of the right arm and leg. He was given phenobarbital and slept until the follow-

ing day when he had entirely recovered. Since then he had noticed transient spells of weakness of the right arm and leg and transient paresthesias involving part or all of the right face, arm or leg; these episodes lasting from 5 to 35 minutes. Five episodes of right facial weakness had occurred, the most recent being in February, 1955. More recently the patient noted deviation of gait to the right. On several occasions he complained of loss of vision as though "a sheet had been passed in front of the eyes." These visual disturbances lasted up to 10 minutes. There had been some difficulty in counting change and expressive aphasia was manifested by difficulty in selecting the proper word. His writing was intermittently illegible. Two weeks before admission the patient suddenly developed respiratory stridor, cyanosis and epistaxis from the right nostril. There was an involuntary inversion of the right foot. The entire episode endured no more than 10 minutes.

The general physical examination was not remarkable. The blood pressure was 160/78. The neurological studies revealed no cranial nerve defect. Pupillary reactions were normal and visual fields were intact to gross testing. There was no papilledema.

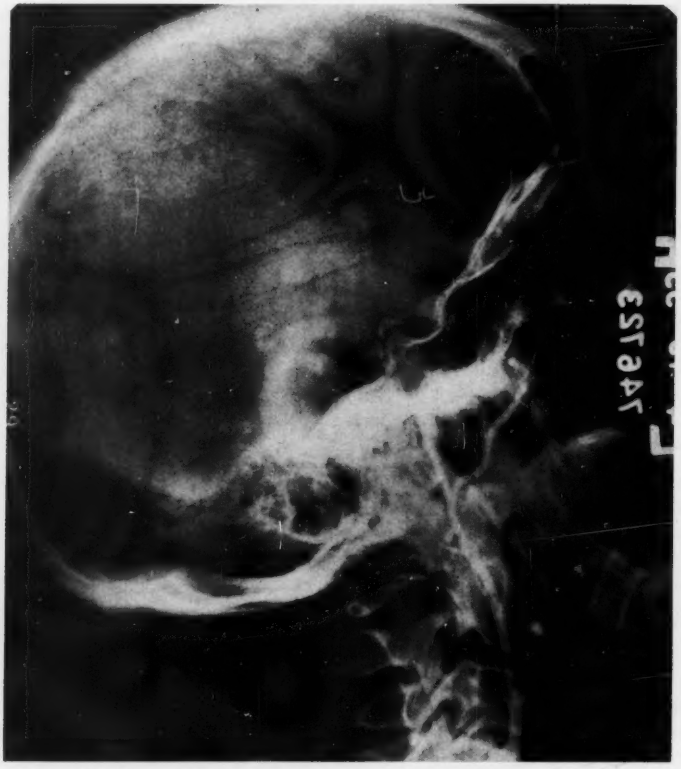

Fig. 3. (Case 2). Left carotid arteriogram demonstrating no patency of the internal carotid artery and little or no evidence of a collateral circulation.

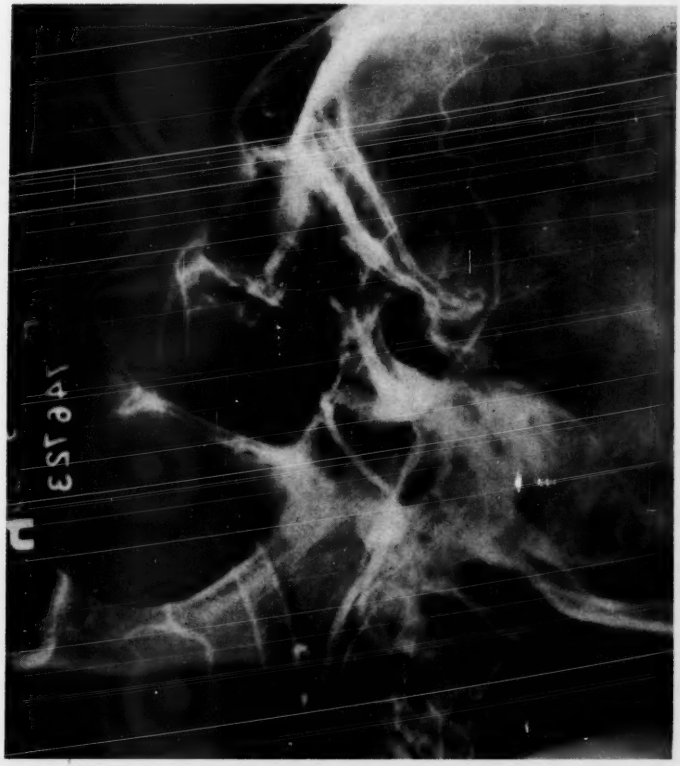

Fig. 4. (Case 2). Right carotid arteriogram showing a well-filled carotid siphon and a collateral blood supply by way of the external maxillary artery and retrobulbar anastomoses. The anterior and middle cerebral arteries can be discerned behind the middle meningeal branches.

No paresis of any muscle group was demonstrated and the gait appeared to be normal. No deficit in touch, pin prick or vibratory sense could be elicited. Position sense was normal, tendon reflexes were symmetrically active and the abdominal reflexes were equal. An equivocal Babinski sign was present on the right. There was no unsteadiness in the Romberg position. Finger-to-nose and heel-to-knee tests were well performed. There were no tremors and the Holmes rebound test was normal.

Routine blood studies and serology were normal. Urinalysis showed a 4 plus sugar. A glucose tolerance test was abnormal but blood sugar levels were controlled by diet. The spinal fluid pressure was 260 (mm., H_2O); there was one cell per cu. mm., no globulin and 3 mg. of protein. Roentgenograms of the skull and the chest were normal. There were hypertrophic changes in the cervical spine.

Bilateral carotid arteriograms showed thrombosis of both internal carotid arteries with good filling of the external carotids, and of the anastomoses with the ophthalmic

artery and siphon on the right side (Figs. 3 and 4). During bilateral cervical sympathectomy the internal carotids were identified as dense hard cords.

Immediately after surgery it was apparent that the patient had developed a right hemiplegia and aphasia. During the next week he recovered, retaining only a slight nominal aphasia and paresis of the leg. There was, however, considerable apraxia and weakness of the right hand. The Babinski and Hoffman signs were present on the right.

The patient was discharged from the hospital but about one week later he again developed a right hemiplegia which in a 24-hour period had shown some improvement.

Case 3. A salesman was first seen at the Cleveland Clinic in 1952, at the age of 55 years, complaining of numbness and pins-and-needles sensations in the hands and feet. In addition, he gave a five-year history of intermittent, dull, aching precordial pain brought on by exertion. On physical examination at that time, he was found to have a mild hypertension of 150/90, mild arteriosclerotic heart disease, and some generalized arteriosclerosis. Six months later, in August of the same year, the patient had one episode of momentary unconsciousness precipitated by coughing and at that time it was believed to be a laryngeal syncope. He was told that he should reduce his activity, use nitroglycerin for the precordial pain, and stop smoking.

He was not seen again until January, 1954, when his complaints were heaviness and numbness in the hands and feet. The patient stated that the complaints had been present intermittently for two years. At the time of admission he stated that 24 hours preceding the onset of weakness in the right leg, he had had numbness and a heavy feeling in the left hand. His face became numb bilaterally and his vision blurred. The patient feared that he had had a stroke. He also stated that during the morning of the day of admission, he had been unable to talk for a few moments and that during recent weeks he had been having memory lapses. His blood pressure was 184/100. Neurological examination revealed an alert, mentally clear patient with intact cranial nerves, a slight weakness of the left hand and arm and an apraxia of the same extremity. There was no sensory deficit. Deep tendon reflexes were slightly hyperactive in the left lower limb. There was no Hoffman or Babinski sign and cerebellar signs were absent. The diagnostic impression was that of multiple, bilateral small cerebral thromboses. The emotional state of the patient was one of facetiousness and exaggerated good feeling suggestive of the "witzelsucht" of forebrain disease. The patient was discharged from the hospital on January 20, 1954, and followed as an outpatient.

On April 15, 1955, the patient was again admitted to the hospital with the complaint of several episodes of weakness in the extremities during the preceding three days. These began with a paresis of the right arm and leg in the early morning hours, which persisted for approximately ten minutes, and prevented his getting to the bathroom. Several more spells, each lasting five to ten minutes, had occurred and were associated with dizziness and with weakness in both legs and arms. He never lost consciousness during any of the episodes. Finally, a spell of generalized weakness and vertigo lasting approximately one-half hour frightened him and prompted his seeking admission to the hospital.

Examination revealed no involvement of the cranial nerves, no weakness and no loss of sensation to touch or pin prick. Deep tendon reflexes were normally active and equal throughout. There was no Babinski sign but a Hoffman was present on the right. The abdominal reflexes were absent. During attacks, the patient claimed inability to move the right arm or leg. The paucity of objective findings, when the patient's complaints were quite pronounced, suggested a hysterical reaction. Later, when the patient became extremely abusive and started to throw articles from his bedside table, the impression was even more firmly established that most of his symptoms were functional. However

two days following these episodes, the patient developed a very obvious spastic paralysis of the left upper and lower extremity. The Babinski and Hoffman signs were present and a positive oral or snout reflex was elicited. The deep tendon reflexes were hyperactive on the left. A slight amimia was present on the right side. Cervical sympathetic blocks produced no change. An electroencephalogram revealed focal dysrhythmias in the right central and parietal area and some abnormalities in the left parietal area.

During the next several days, the patient had frequent episodes of weakness on the right side, associated with feelings of numbness and awkwardness in an arm or leg, or in both. He received several stellate blocks, which did not produce any changes in the symptoms.

On April 29, the patient became quite uncommunicative and was found to have a spastic quadriparesis. The Babinski sign was present bilaterally. He had a nominal aphasia but moved his eyes and protruded his tongue on command. On May 2, bilateral carotid arteriograms revealed thrombosis of both internal carotid arteries. A bilateral cervical symphathectomy was performed. Both internal carotid arteries were nonpulsating and firm, the right less so than the left. The patient did not respond following surgery and remained in decerebrate rigidity until he died on May 25, 1955.

The laboratory studies throughout the patient's visits to the hospital always had been within normal limits. The serology was negative on three occasions. The patient never showed evidence of diabetes or renal disease. Roentgenograms of the chest and skull were normal. Roentgenograms of the lumbar spine revealed some hypertrophic changes. Also noted were calcifications in the abdominal aorta and iliac vessels. Electrocardiograms, taken on several occasions, revealed evidence of old posterior myocardial infarction with no change during the period 1952 to 1955. Postmortem examination revealed complete thrombosis of long standing of the left internal carotid artery in the cervical portion as well as in the siphon. The right internal carotid artery was occluded by an atherosclerotic plaque just above the common carotid bifurcation. There was, however, a small lumen still present at this site which was estimated as being about 10 per cent of normal patency. The middle cerebral artery on the same side was not involved but the right anterior cerebral artery contained several firm red clots.

Both frontal lobes were symmetrically softened to palpation, and section revealed a large area of necrosis in the distribution of both anterior cerebral arteries. There were symmetrical areas of necrosis in the basal ganglia encroaching upon the genu of each internal capsule. Some of the involved areas presented fresh cyst formations and others a translucency indicating lesions of longer standing. Sections through the brain stem demonstrated no gross abnormality. The vertebral, basilar and posterior communicating arteries were widely patent with little or no evidence of atherosclerosis.

Comment

The cases reported here are obviously inadequate to define fully a syndrome of bilateral internal carotid artery thrombosis if such a syndrome actually exists. However significant findings are demonstrated and an attempt will be made to correlate them.

As stated by Fisher[1] and Frøvig,[6] dementia is a prominent feature. One of our patients (Case 2) did not demonstrate such aberration to his wife or to the examiners because it was either in an inchoate state or was not present at all. This facet of the symptomatology requires a larger series for evaluation. How-

ever it appears from our studies and those of Frøvig that no specific pattern of a psychosis results from the altered blood supply and that the psychotic changes, whatever may be their nature, do not differ from those resulting from unilateral occlusion of the internal carotid artery.

Transient hemiplegia, first appearing on one side and then on the other, or a paraplegia probably is the most telltale of all symptoms in bilateral occlusion. Interestingly enough, hemiplegia first developed in all three of our cases on the right side, lending support to the statement that thrombosis is more common in the left carotid artery. This figure does not consider the incidence of right-handed people in the population or the relative paucity of symptoms in right cerebral lesions. Transient paraplegia of the lower limbs which existed in our first case is consistent with the reduction of blood flow through both anterior cerebral arteries. Frøvig's patient also complained of severe weakness of the lower extremities.

Bilateral visual disturbances of a transient nature occurred in all three patients. These could hardly be attributed to disturbances of the visual cortex which is supplied chiefly by the posterior cerebral circulation; it is possible that these rather ephemeral visual symptoms may be due to the readjustments in the blood supply of the eyeball made necessary by the retrograde blood flow in the ophthalmic arteries.

Transient sensory phenomena such as paresthesias of the face and extremities were present bilaterally in two of our patients and are also to be considered as being suggestive of bilateral occlusion if such sensory disturbances are found on both sides of the body.

Alvarez[7] recently brought to attention the significance of repeated minor episodes of focal cerebral defect producing transitory symptoms and which are regarded as being "little strokes" or vascular spasms prodromal to a permanent cerebral lesion. It is probable that because of the similarity of symptoms in this syndrome to those of thrombosis of the internal carotid artery, either unilateral or bilateral, many cases of the latter condition remained without a correct diagnosis in the pre-arteriographic era.

At present the diagnosis depends on surgery and arteriography, or on post-mortem examination. Experience with palpation of the thrombosed arteries in the neck or pharynageal wall has been highly unsatisfactory. Actually, manipulation of these vessels during arteriography or cervical sympathectomy may precipitate the development of more neurological defects, as it did in two of our patients.

The frequency of bilateral thrombosis of the internal carotid artery is unknown. We are certain that its presence in the ambulatory patient would hardly have been suspected a few years ago. There is no precise manner of establishing the time of the onset of the occlusions, whether these be unilateral or bilateral, because the symptoms are so variable and fluctuate in most unpredictable fashion.

The one outstanding and highly suggestive clinical evidence for thrombosis of both internal carotid arteries is the presence of evanescent and bilateral signs of defect in motor, sensory and language functions of the cerebral cortex. The frequently overlooked or misinterpreted mental changes are of great importance and should be the subject of a special study in themselves.

The authors recognize that pathologic material was not available to allow a comprehensive study of all the marked changes that take place in cerebral tissues when both internal carotid arteries are occluded by vascular disease. Because of the extreme variability of the caliber and arrangement of the cerebral vessels that prc vide collateral circulation in and about the circle of Willis in the human being, it is probable that both clinical signs and pathologic changes can never be so stereotyped as to provide a clear syndrome in this disease. The demonstration of occlusion by angiography and the presence of cordlike internal carotid arteries on surgical exposure are sufficient verification of the diagnosis. The more and more frequent application of angiography of the cerebral circulation will probably demonstrate that this vascular disorder is not an infrequent cause of mental and neurological disease.

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PROBLEMS IN THE DIFFERENTIATION OF THE MILK-ALKALI (BURNETT'S) SYNDROME AND HYPERPARATHYROIDISM, ILLUSTRATED BY TWO CASE REPORTS

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THE milk-alkali (Burnett's) syndrome and hyperparathyroidism under certain circumstances may be practically indistinguishable clinically.[1] Those special circumstances are illustrated in the two case histories that will be presented following a brief comparison of the characteristics, causes, and courses of the two diseases.

Burnett's syndrome is characterized by hypercalcemia without hypercalciuria (Table). It does not cause skeletal damage. The etiologic factor is the excessive intake of milk and absorbable alkali. The condition eventually results in renal failure, but just before renal failure, hypocalciuria becomes evident in an alkaline urine.

TABLE

Anticipated Findings in Milk-Alkali (Burnett's) Syndrome and in Hyperparathyroidism with Associated Renal Insufficiency

Factors	Milk-Alkali (Burnett's) Syndrome	Hyperparathyroidism with Associated Renal Insufficiency
Serum calcium	Increased	Increased
Serum phosphorus	Normal	Normal or increased
CO_2-combining power	Elevated or normal	Normal or low
Urinary pH	High (above 7.0)	Low (below 7.0)
Urinary calcium excretion	Low	High (late in course of disease it may be low)
Cystic bone disease	Absent	Absent in more than 50% of cases
History of intake of milk and absorbable alkali	Present	Absent

Hyperparathyroidism is characterized by hypercalcemia with high urinary calcium excretion, which eventually results in renal failure. However, when renal failure occurs as a late complication of the disease, the low serum phosphorus and the hypercalciuria may disappear, and as in Burnett's syndrome, hypercalcemia without hypercalciuria exists (Table). In about one third of the patients having hyperparathyroidism there is skeletal damage, and pathognomonic roentgenographic findings are osteitis fibrosa cystica and absence of the dental lamina dura. The etiologic factor generally is a tumor of one or more parathyroid glands, which when aberrant may be situated somewhere in the mediastinum.

CASE REPORTS

Case 1. A 63-year-old farmer was first seen on April 26, 1954. His presenting complaint was that of daily "heartburn" of many years' duration. His appetite had become poor and he had lost 5 pounds in weight during the previous month. He had muscular weakness, constipation, moderate thirst, and nocturia.

Findings on physical examination were not unusual. However, a KUB roentgenogram disclosed a semicircular opaque shadow within the left renal pelvis. The blood-urea content was 150 mg./100 ml. The blood-urea clearance rate was 14 per cent at the end of the first hour and 12 per cent at the end of the second hour. The red blood cell count was 3,380,000/cu. mm. and the hemoglobin content was 9.2 Gm./100 ml. The initial serum calcium was 15.9 mg./100 ml. and the initial serum phosphorus 4.0 mg./100 ml. Subsequent determinations of serum calcium were 16.0, 14.9 and 15.2 mg./100 ml., and of serum phosphorus 4.0, 3.2 and 1.6 mg./100 ml. The total serum protein content was 7.4 Gm./100 ml. with an albumin of 4.5 Gm. and a globulin of 2.9 Gm./100 ml. The urine had a specific gravity of 1.012 with a pH of 7.5. A urinary calcium excretion on the third day of a fixed calcium intake of 140 mg./24 hours, was 450 mg./24 hours (the upper normal value in our laboratory on this diet is 150 mg./24 hours).

Because of the hypercalcemia with hypercalciuria, hyperparathyroidism was considered the most likely diagnosis and the most likely cause of the renal insufficiency. On careful questioning, the patient admitted the consumption of milk but denied the use of absorbable alkali. The serum phosphorus level was relatively low—lower than ordinarily would be expected in a patient with this degree of renal insufficiency, particularly the one determination of 1.6 mg./100 ml. The finding of this low value for serum phosphorus is not explicable, particularly since subsequently a similarly low value was obtained. However, the skeletal damage that frequently is found in hyperparathyroidism was absent; skeletal roentgenographic findings were normal; and the dental lamina dura was present. An intravenous calcium-load test, according to the technic of Howard,[2] was performed. The control excretion of phosphorus was 80 mg./24 hours on the third day of a low-phosphorus diet. On the fourth day 30 mg. of calcium gluconate per kilogram of body weight was given in saline over a four-hour period. During the infusion of calcium the hourly serum phosphorus determinations were as follows: Fasting, 2.2 mg.; one hour, 2.0 mg.; two hours, 2.1 mg.; three hours, 1.9 mg.; and four hours, 2.4 mg./100 ml. The total urinary phosphorus excretion on that day was 60 mg. The test was evaluated as follows: A normal test is accompanied by a rise in serum phosphorus and a fall in urinary phosphorus. Patients with parathyroid tumor show a fall in serum phosphorus and a rise

in urinary phosphorus. In this patient there was a fall in serum phosphorus but no rise in urinary phosphorus.

On May 12, 1954 (16 days after the initial visit), the neck was explored for a parathyroid tumor. No parathyroid tumor or hyperplasia was found. Hypercalcemia persisted and on October 14, 1954, the mediastinum was thoroughly searched for a parathyroid tumor but none was found. It was then learned that the patient had carefully concealed the fact that with the daily consumption of a large amount of milk he also had for several years eaten "Tums" in large quantities in an attempt to control the "heartburn." This practice was immediately discontinued, and on October 18, 1954, the serum calcium was 11 mg. and the serum phosphorus 4 mg./100 ml., with a total serum protein of 7.1 Gm./100 ml. The serum calcium on June 9, 1955, was 9.9 mg. with a serum phosphorus of 3.3 mg./100 ml. and a blood urea of 24 mg./100 ml. The blood-urea clearance rate had increased to 47 per cent the first hour and 41 per cent the second hour (formerly, 14 and 12 per cent respectively).

Comment: This patient now is regarded as having had Burnett's syndrome and not hyperparathyroidism. The excessive intake of milk and absorbable alkali for a period of years, and the hypercalcemia so induced led to renal insufficiency but not to hypocalciuria as is usually present in Burnett's syndrome. The urinary pH value of 7.5 persisted until the patient discontinued taking absorbable alkali, whereupon the urinary pH fell to 6.8. The prompt disappearance of the hypercalcemia and the fall both in blood urea and in urinary pH with the discontinuance of milk and alkali favor this diagnosis, which is further supported by the negative surgical exploration of the neck and of the mediastinum for parathyroid tumor.

The normal skeletal findings can be explained on the basis of an excessive intake of milk that presumably protects the skeleton from decalcification, but the important consideration from a clinical point of view is that the absence of bone disease tends to indicate the presence of Burnett's syndrome. It is of course clearly recognized, as mentioned earlier, that only about one third of the patients with hyperparathyroidism have skeletal damage, so that its absence in this case did not exclude hyperparathyroidism as a cause of hypercalcemia. Patients with hyperparathyroidism and renal insufficiency from nephrocalcinosis will have hypercalcemia without a low serum phosphorus and eventually will lose their hypercalciuria (illustrated in Case 2). This combination is far more common than is hyperparathyroidism with skeletal damage either with or without renal disease.

Case 2. A 26-year-old office worker was first seen on February 15, 1955. His presenting complaint was that of aching discomfort in his heels, and weakness in the knees of four years' duration. He stated that on bending forward his knees felt stiff and that they were painful on the anterior surfaces. His thirst was extreme and he had nocturia four to six times each night. He stated that he consumed large quantities of milk, from 2 to 5 quarts daily, and that he had done this for a number of years. There was no history of excessive consumption of vitamin D or alkali. There was no past history of renal disease.

Physical examination disclosed extreme reflex excitability of all tendon reflexes, yet muscular tone was flabby. Despite his muscular wasting he was able to walk five to eight miles each day. His hand grip was above normal. There was clubbing of the fingers, a rare occurrence in hyperparathyroidism. Lateral nystagmus was present. Roentgenographic examination revealed cystic changes in the long bones, diffuse mottling of the

skull with a "ground-glass" appearance, and absorption of the dental lamina dura. The total serum calcium was 13.8 mg. and serum phosphorus was 7.2 mg./100 ml. Alkaline phosphatase measured 11.2 Bodansky units. Recheck serum calcium and serum phosphorus were 12.0 mg. and 7.3 mg./100 ml., respectively, and alkaline phosphatase measured 11.7 Bodansky units. Numerous subsequent determinations for serum calcium and serum phosphorus disclosed levels comparable to those mentioned; serum phosphorus levels were as high as 8.3 mg./100 ml. The total serum protein was 9 Gm./100 ml., with an albumin of 4.6 Gm. and a globulin of 4.4 Gm./100 ml. A recheck total serum protein measured 7.9 Gm. with an albumin of 3.8 Gm. and a globulin of 4.1 Gm./100 ml. The plasma creatinine was 6.4 mg./100 ml., and the blood urea 189 mg./100 ml. The CO_2-combining power was 21.2 volumes per cent, and plasma chlorides were 544 mg./100 ml. Hemoglobin content was 12.0 Gm./100 ml., with a red blood cell count of 4,630,000/cu. mm., and a total cell volume of 40 ml./Kg. of body weight. The blood-urea clearance rate was 14 per cent at the end of the first hour and 13 per cent at the end of the second hour. On a 12-hour night urine collection, the urine had a specific gravity of 1.008, with a pH of 6.0 and a protein excretion of 0.9 Gm. Urinary calcium excretion on the third day of a controlled calcium diet was 67 mg./24 hours (upper normal 150 mg./24 hours).

The diagnosis of primary hyperparathyroidism was considered because of the hypercalcemia, the cystic bone disease with absence of dental lamina dura, the elevated alkaline phosphatase and the renal failure. The renal failure was considered to be secondary to the hypercalcemia and was regarded as resulting from nephrocalcinosis. There were no hypertension, significant anemia, or proteinuria, which made it seem unlikely that primary renal disease was the problem. Furthermore, patients with secondary hyperparathyroidism usually are found not to have bone disease with this degree of severity nor do they present hypercalcemia. The diagnosis of Burnett's syndrome was considered, but it was excluded by the presence of bone disease with destruction of dental lamina dura, osteitis fibrosa cystica, and a high alkaline phosphatase. Bone disease does not occur in typical Burnett's syndrome. Furthermore, there was no history of excessive consumption of alkali, and it is necessary that absorbable alkali be consumed with excessive amounts of milk in order to cause hypercalcemia. The urinary pH of 6.0 and the low CO_2-combining power also were incompatible with Burnett's syndrome.

The absence of hypercalciuria and the presence of an elevated serum phosphorus were believed to be due to renal failure induced by the hypercalcemia of primary hyperparathyroidism. During an intravenous calcium-load test, performed as in Case 1, the serum phosphorus fell from a level of 7.0 mg. to a level of 6.2 mg./100 ml., and the urinary phosphorus rose from a control excretion level of 70 mg. to a level of 93 mg./24 hours. Because of this and other findings indicating the diagnosis of primary hyperparathyroidism, an exploratory operation was performed on May 13, 1955, three months after the initial visit. A parathyroid adenoma, chief cell in type, was found on the left upper parathyroid; it measured 3 by 1.5 by 1 cm. Following the removal of the parathyroid tumor the serum calcium level fell to 7.0 mg./100 ml., resulting in active tetany that required administration of calcium and vitamin D. Blood urea fell to 57 mg./100 ml. on the fourth postoperative day. A few days later the patient was discharged and was advised to continue taking vitamin D, 50,000 units four times daily, and calcium lactate, 6 drams per day. This therapy allowed the blood calcium to reach levels of approximately 8.5 to 9 mg./100 ml. in four weeks.

Discussion

It is believed that the two cases clearly present many of the problems inherent in differentiating between milk-alkali syndrome and hyperparathyroidism. The first patient, who had consumed milk and alkali for a number of years, had renal failure, hypercalcemia, an alkaline urine, and, despite renal failure, hypercalciuria. The last is an extraordinary occurrence in Burnett's syndrome. Bone disease was absent, as it might be in either Burnett's syndrome or primary hyperparathyroidism. The prompt disappearance of azotemia and the fall to normal of the serum calcium level upon the discontinuance of absorbable alkali was followed by a partial recovery and an improvement of renal function. The second patient, with primary hyperparathyroidism, had renal failure of a degree sufficient to lower the urinary calcium excretion, on a controlled diet, to 67 mg./24 hours. This is the lowest 24-hour urinary excretion of calcium in any case of hyperparathyroidism that has been recorded in the literature. The urine was always acid in reaction. The bone lesions, with cystic changes in the skull and disappearance of the dental lamina dura, were of a degree incompatible with Burnett's syndrome or with secondary hyperparathyroidism. The absence of anemia, of proteinuria, and of hypertension was incompatible with a diagnosis of primary renal failure with secondary hyperparathyroidism.

Hypercalcemia regardless of its cause is accompanied by polyuria, nocturia, muscular weakness, and anorexia. The renal insufficiency seen in Burnett's syndrome is in no way different from that seen in other disorders in which hypercalcemia has led to nephrocalcinosis. Patients with "nephrocalcinotic renal failure" usually do not appear to be ill. The elevated urinary pH in the presence of hypercalcemia is a point in favor of the diagnosis of Burnett's syndrome when there is no history of excessive intake of milk and absorbable alkali.

It has been suggested that Burnett's syndrome might be an atypical hyperparathyroidism. This suggestion appears to be untenable for several reasons: Hypercalcemia and with it renal failure, hypocalciuria, and high urinary pH, develop in only a few patients who ingest milk and alkali for treatment of duodenal ulcer or hyperacidity. Furthermore, discontinuance of the milk and alkali leads to a prompt fall in the urinary pH, increased urinary excretion of calcium, a fall in serum calcium and, within a few days, reduction in blood urea. Such quick changes would not be expected in hyperparathyroidism, either primary or secondary in type. A negative parathyroid and mediastinal exploration (as in Case 1) further supports the nonparathyroid source of the hypercalcemia in Burnett's syndrome.

Summary

Findings in two cases, one of milk-alkali (Burnett's) syndrome and the other of primary hyperparathyroidism, are reported to illustrate the occasional difficulties in differentiating these conditions. The presence of hypercalciuria in the patient having Burnett's syndrome and its absence in the patient having hyper-

parathyroidism are rare occurrences. In the latter patient, the phenomenon apparently was a manifestation of a severe degree of renal failure.

The responses to an intravenous calcium-load test were of diagnostic value in both patients, showing no change in serum phosphorus and lowered urinary phosphorus in the patient having Burnett's syndrome; and a lowered serum phosphorus and an elevated urinary phosphorus in the patient having hyperparathyroidism. The response was not compatible with a diagnosis of hyperparathyroidism in the patient with Burnett's syndrome; but in the patient having primary hyperparathyroidism, the response was compatible with the latter diagnosis.

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ANNOUNCEMENT

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Dr. Rudolph H. Kampmeier, professor of medicine, Vanderbilt University School of Medicine, will be the fifth annual Physician-in-Chief pro tempore on December 15, 16, and 17, 1955. During his tenure, Doctor Kampmeier will devote his entire time to the teaching program of the Fellows in Medicine. A schedule of daily clinics, lectures, and seminars has been arranged. Members of the medical profession are cordially invited to attend.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

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Wednesday, October 26, 1955

Morning Session

8:00- 8:55 a.m.	.	Registration
		Morning Session . . . . . E. N. COLLINS, M.D., PRESIDING
8:55- 9:00 a.m.	.	Welcome . . . . . F. A. LEFEVRE, M.D.
9:00- 9:20 a.m.	.	Newer Techniques in the Roentgen Examination of the Esophagus . . . . . A. S. TUCKER, M.D.
9:20- 9:40 a.m.	.	Esophagoscopy: Indications; Current Methods and Conservative Treatment of Esophageal Disease . . . . H. E. HARRIS, M.D.
9:40-10:00 a.m.	.	The Surgeon's Appraisal of Symptoms; The Surgical Treatment of Esophageal Abnormalities . . . . . D.B. EFFLER, M.D.
10:00-10:10 a.m.	.	Cobalt Bomb Treatment in Carcinoma of the Esophagus . . . . . R. A. HAYS, M.D.
10:10-10:30 a.m.	.	Coffee Break
10:30-11:00 a.m.	.	Exfoliative Cytology of the Gastrointestinal Tract . . . . . J. B. KIRSNER, M.D.*
11:00-11:30 a.m.	.	Decubitus Technique in Cholecystography; Intravenous Cholangiography; Cholographin . . . . . R. E. WISE, M.D.*
11:30-11:45 a.m.	.	Problems of Cholelithiasis; Value of Cholangiograms at Time of Surgery . . . . . S. O. HOERR, M.D.
11:45-12:15 p.m.	.	Questions and Answers
12:30 p.m.	.	Luncheon—Courtesy Bunts Institute
		Afternoon Session . . . . . H. R. ROSSMILLER, M.D., PRESIDING
1:45- 2:15 p.m.	.	Medical Management of Peptic Ulcer, Including the Use of Anticholinergic Drugs and X-ray Therapy . J. B. KIRSNER, M.D.*
2:15- 2:45 p.m.	.	Changing Concepts in the Surgical Management of Peptic Ulcer, Including the Use of Vagotomy and Hemigastrectomy for Duodenal Ulcer . . . . . GEORGE CRILE, JR., M.D.
2:45- 3:00 p.m.	.	Gastric Cancer: New Classification; Is a More Hopeful Outlook Justifiable? . . . . . S. O. HOERR, M.D.
3:00- 3:15 p.m.	.	Coffee Break
3:15- 3:45 p.m.	.	Acute and Chronic Pancreatitis; Diagnosis and Medical Management . . . . . F. J. OWENS, M.D.
3:45- 3:55 p.m.	.	Surgery of the Pancreas . . . . . GEORGE CRILE, JR., M.D.
3:55- 4:25 p.m.	.	Differential Diagnosis of Jaundice; Present Status of Liver Function Tests . . . . . C. H. BROWN, M.D.
4:25- 5:00 p.m.	.	Questions and Answers

**Guest speaker.*

Thursday, October 27, 1955

		Morning Session . . . . . C. H. BROWN, M.D., PRESIDING
9:00- 9:30 a.m.	.	Liver Biopsy; Laennec's Cirrhosis and Portal Hypertension Syndrome . . . . . H. R. ROSSMILLER, M.D.
9:30- 9:40 a.m.	.	Current Surgical Procedures Used in the Treatment of Esophageal Varices . . . . . GEORGE CRILE, JR., M.D.
9:40-10:00 a.m.	.	Newer Roentgen Techniques Used in Gastrointestinal Examination, Including the Demonstration of Jejunal Ulcer, Diverticulitis, and Polypi in the Colon . . . . . J. C. ROOT, M.D.
10:00-10:20 a.m.	.	Coffee Break
10:20-10:50 a.m.	.	Amebiasis: Incidence, Symptoms; Use of Newer Drugs . . . . . C. H. BROWN, M.D.
10:50-11:20 a.m.	.	Regional Enteritis: Current Concepts . . H. R. ROSSMILLER, M.D.
11:20-12:00 noon	.	Questions and Answers
12:15 p.m.	.	Luncheon—Courtesy Bunts Institute
		Afternoon Session . . . . . E. N. COLLINS, M.D., PRESIDING
2:00- 2:15 p.m.	.	The Use of Splanchnic and Intercostal Block Anesthesia in Diagnosis . . . . . D. E. HALE, M.D.
2:15- 2:30 p.m.	.	Staphylococcus-Pseudomembranous Enterocolitis (Coagulase Positive); Bacteriologic Studies . . . . . ALFRED REICH, B.S.
2:30- 3:00 p.m.	.	Diagnosis and Medical Management of Chronic Nonspecific Ulcerative Colitis . . . . . E. N. COLLINS, M.D.
3:00- 3:15 p.m	.	Coffee Break
3:15- 3:45 p.m.	.	Surgical Treatment: Chronic Nonspecific Ulcerative Colitis; Total Colectomy and Ileostomy in One or Two Stages; New Type of Ileostomy . . . . . R. B. TURNBULL, Jr., M.D.
3:45- 4:30 p.m.	.	Significance and Treatment of Polyps; Cancer of Colon and Rectum . . . . . .R. B. TURNBULL, JR., M.D.
4:30- 5:00 p.m.	.	Questions and Answers

Guest Speakers

JOSEPH B. KIRSNER, M.D., Ph.D.: Professor of Medicine, The University of Chicago, The School of Medicine, Chicago, Illinois.

ROBERT E. WISE, M.D.: Department of Roentgenology, Lahey Clinic, Boston, Massachusetts.

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